Mainstream Smoke Constituent Yields and Predicting Relationships from a Worldwide Market Sample of Cigarette Brands: ISO Smoking Conditions.

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ABSTRACT

The study objective is evaluation of a benchmark approach for predicting mainstream smoke constituent machine-yields for conventional cigarette brands from worldwide markets. Results for ISO smoke yields support the validity of benchmarking when brands, for which yields are to be predicted, have design characteristics within boundaries established by the exploratory brands. Yields of ISO-method mainstream smoke constituents were generally well described by weighted least squares regression relationships with ISO tar ($R^2 > 0.80$ and coefficient p-values < 0.05). The impact of the varied chemical composition of cigarette tobaccos from different regions on smoke constituent yields was recognized. Mainstream smoke nitrogen oxides and tobacco-specific nitrosamine (TSNA) yield prediction relationships improved by including tobacco nitrate or TSNA concentration factors in respective independent parameters. For carbon-filter brands, inclusion of a carbon factor improved the predicting relationships for several vapor-phase constituents. Relationships were validated with a subset of additional validation brands. Greater than 90% of the validation brands' smoke chemistry yields were within the 95% prediction intervals. Average differences between measured and predicted yields were generally within the range of one to two measurement standard deviations. The estimation methods proposed relate to machine-smoking conditions and are not intended to reflect the actual exposure of any given consumer to smoke constituents.

Key Words: benchmarking, prediction relationships, prediction intervals, mainstream smoke constituents, smoke yield variation

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Abbreviations: ASTM, American Society for Testing and Materials; IARC, International Agency for Research on Cancer; IEC, International Electrotechnical Commission; ISO, International Organization for Standardization; NAB, N-nitrosoanabasine; NAT, N-nitrosoanatabine; NNK, 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-nitrosonornicotine; TSNA, tobacco-specific nitrosamine

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INTRODUCTION

The goal of this work is to describe the results of statistical methods for estimating the deliveries of a variety of mainstream cigarette-smoke constituents generated under International Organization for Standardization (ISO) machine-smoking conditions. The cigarette brands were from worldwide markets. In future reports, results will be presented for estimating smoke constituent yields under "Massachusetts" smoking conditions, as defined by the Massachusetts Department of Health (Massachusetts, 1997) and "intense" smoking conditions, as defined by Health-Canada (Canada, 2000a). The estimation methods proposed relate to machine-smoking conditions and are not intended to reflect the actual exposure of any given consumer to smoke constituents.

The tobacco industry has provided cigarette smoke tar, nicotine, and carbon monoxide yield data for various regulatory agencies for many years. For mainstream smoke generation and collection, cigarette manufacturers in the United States are required to use the Federal Trade Commission (FTC) machine method for tar, nicotine, and carbon monoxide yield reporting (Federal Register, 1967 and 1980). Internationally, the ISO machine method is recognized as the standard for determining cigarette tar, nicotine, and carbon monoxide yields (ISO 3402; ISO 3308; ISO 4387; ISO 10315). The FTC and ISO machine-smoking methods for determining mainstream smoke tar, nicotine, and carbon monoxide yields have been standardized and validated through extensive inter-laboratory (collaborative) study. More recently, regulations have been adopted or proposed for reporting the yields of other specific smoke chemicals found in mainstream or sidestream cigarette smoke (Brazil, 2001; World Health

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Organization, 2000a).

Cigarette smoke is a complex chemical mixture. Nearly 4000 chemical constituents have been identified in mainstream cigarette smoke (Dube and Green, 1982; Roberts, 1988). These individual chemical compounds and elements, as opposed to tar which is a composite of chemicals, are referred to as smoke constituents. Considerable research has been reported on cigarette smoke constituents that are identified as potentially toxic (IARC, 1986 and 1999; U.S. Department of Health and Human Services, 1989; Hoffmann, 1993). Smith et al (1997, 2000, and 2001) published comprehensive literature reviews of IARC Group 1, 2A, and 2B carcinogens found in mainstream cigarette smoke. Numerous publications are also available that review standard machine-smoking test methods, alternative smoking methods, and the relevancy of machine-smoking test protocols to human smoking behaviors and cigarette smoke exposure (World Health Organization, 2000b; Borgerding, 1997; Baker, 1999; National Cancer Institute, 1996 and 2001; Federal Register, 1997).

The current work is not meant necessarily to imply relevancy to a particular human smoking behavior or any one consumer's potential exposures to smoke constituents. Understanding the wide range of adult consumer smoking behaviors and potential exposures to smoke requires clinical research. A population study of exposure of U.S. adult smokers to cigarette smoke is in progress and will add to this understanding (Kinser et al, 2001; Walk et al, 2001). Relationships between machine-generated smoke component yields, however, can provide guidance in studies of biological systems and cigarette smoke.

The reporting of individual smoke constituent yields raises a number of issues.

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While the FTC and ISO machine methods are recognized standards for the generation and collection of mainstream cigarette smoke (and determination of tar, nicotine, and carbon monoxide), there are no internationally recognized and standardized methods for the analysis of other smoke constituents. The Canadian Government has stipulated both machine-smoking conditions and smoke constituent analytical methods in its Tobacco Act Reporting Regulation for cigarette products marketed in Canada (Canada, 2000a). This is the only known requirement for specific analytical methods within a regulation. Without standardized analytical methods, comparison of smoke constituent yields for various cigarette products which were determined by different analytical methods remains challenging. Reported cigarette constituent yield differences or could be due to analytical method differences rather than brand characteristics. All analyses reported in this work were performed by a single laboratory.

Benchmarking, as used here, encompasses the testing of a set of cigarette brand samples having design features representative of the marketplace. Functional relationships are then established between the yields of each smoke constituent and the predicting variables. The predicting variables are generally tar, nicotine, or carbon monoxide deliveries. The functional relationships are subsequently used to predict constituent yields for other cigarette brands.

The study reported here will not have been the first to demonstrate the potential utility of a benchmarking approach. Other studies have developed or proposed relationships between smoke chemistry yields (Jenkins et al, 1983; Chepiga et al, 2000; Seeman et al, 2003). An extensive benchmark study was performed by four U.S. tobacco companies in 1999 in cooperation with the Massachusetts Department of

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Public Health (MDPH) (Borgerding et al, 2000). Mainstream smoke constituent yields of brands representative of the U.S. market were determined at smoking conditions defined by the MDPH (Massachusetts, 1997). Functional relationships between tar, nicotine, or carbon monoxide and individual smoke constituents demonstrated predictability for other similarly designed brands. An indirect application of benchmarking is found in the Canada Tobacco Act Reporting Regulation (Canada, 2000b). The regulation allows for use of linear functional relationships between tar or nicotine and each of the smoke constituents specified in the regulation. The current study is unique, however, in that it includes brands marketed in a wide distribution of geographical regions with analyses for mainstream tar, nicotine, carbon monoxide and forty-two other smoke constituents

Benchmarking necessitates that brands for which smoke constituent yields are to be predicted have designs that are within the range of the samples used to develop the functional relationships. Design parameters include tobacco blend, tobacco weight, filter ventilation level, and cigarette paper permeability, for example. The functional relationships developed in this study are known to be applicable to brands of the Philip Morris companies that are within the design range defined by the study cigarettes. The approach and statistical treatment of data used in this work would be applicable to other studies of cigarette mainstream smoke constituent yields.

MATERIALS AND METHODS

Cigarettes

Philip Morris commercial brands from various international market regions were tested. Forty-eight filtered brands were selected to include a range of cigarette design

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features and tar categories available in those regions. Most brands were blended cigarettes consisting primarily of bright (flue-cured), burley, and oriental tobaccos and containing some expanded tobacco, reconstituted-tobacco sheet, or processed tobacco stems. Four brands contained primarily bright tobaccos. Nine brands included 14 to 50 mg of activated carbon (also referred to as activated charcoal) in their filter construction. ISO machine-method tar yields ranged from 1 to 14 mg per cigarette. Brands were sampled at fourteen production facilities in late 1999. Table 1 is a summary of design and market characteristics for these cigarette brands.

Table 1. Cigarette market and design characteristics

Characteristic	Ranges
Brands	48 brand styles (15 brand families)
Philip Morris production regions [1]	USA, Latin America, Asia Pacific, Japan, EU, CEMA
ISO machine-method tar yield	1 - 14 mg/cig
Filter types [2]	CA, CA/carbon (three types), concentric paper .
Filter ventilation	0 - 80%
Cigarette length	68 - 100 mm
Cigarette circumference	Slim (~ 23 mm) and standard (~ 25 mm)
Cigarette paper permeability [3]	9 - 87 CORESTA Units
Menthol flavoring	5 menthol, 44 non-menthol
Tobacco weight	0.49 - 0.89 g/cig
Tobacco blend	Category I: All bright tobacco-based (4 brands) Category II (component approx. inclusion): bright, to 50%; burley, to 40%; oriental, to 20%; expanded tobacco, to 55%; processed tobacco sheet, to 30%; processed tobacco stem, to 25%
Packaging	41 hard pack, 7 soft pack

(1) EU = European Union, CEMA = Central Europe, Middle East, Africa. (2) CA = cellulose acetate, CA/carbon is a filter containing both a CA section and a section with carbon on CA. (3) CORESTA Unit (CU) = air flow, cc/min, passing through a 1 cm^2 test apparatus surface at 1.0 kPa pressure.

The study used a split-sample analysis plan. Forty cigarette samples, including thirty-nine commercial brands and the University of Kentucky 1R4F reference cigarette (Davis et al, 1984), made up the exploratory sample group. The other nine commercial brands and the 1R4F reference cigarette were in the validation sample group. The validation group included cigarettes from a range of tar yields and region representation. This group was tested after completion of the exploratory-group testing. The

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exploratory-group data were used to develop the functional relationships. The validation-group data provided independent assessments of the predictive strength of the functional relationships. The 1R4F reference cigarette was included with each sample group for consistency comparisons and was not included in functional relationship development.

Mainstream Smoke Generation and Constituent Analyses

The study was performed at ISO machine-smoking conditions of 35-mL puff volume, 2-s puff duration, and 60-s puff interval. Cigarette samples were conditioned according to ISO Standard 3402 (1999). Twenty replicates were analyzed for tar, nicotine, and carbon monoxide yields. Seven replicates were analyzed for mainstream smoke constituent yields and for smoke "pH." The "pH" of smoke is denoted in quotes to indicate that the measurements are empirical and dependent upon the conditions under which they are made (Rodgman, 2000).

Labstat International Inc. (Kitchener, Ontario), an ISO/IEC 17025-accredited commercial laboratory, conducted the machine smoking, smoke constituent analyses, and smoke "pH" analyses under contract to PM USA. The mainstream smoke constituents analyzed for this study were representative of those included in several current government regulations (Brazil, 2001; Canada, 2000a). Details of analytical methods used by the laboratory can be found in current Health Canada (HC) regulations (Canada, 2000b) or by contacting Health Canada's Tobacco Control Programme (P.L. 3506C, Ottawa, Canada, K1A 0K9). Guidance references cited below are those provided within the HC Official Methods. Corresponding HC test method numbers are provided in parentheses. Outlier statistics (ASTM, 1994) were

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applied to all data.

Tar, nicotine, and carbon monoxide (T-115) were determined according to the relevant ISO standards (ISO 3308, ISO 3402, ISO 4387, ISO 8454, ISO 10315, and ISO 10362-1). Nicotine and water were determined gravimetrically from isopropanol extracts of total particulate matter (TPM) retained by the smoke collection pad. Tar was calculated from the weight of TPM less the weights of water and nicotine. Carbon monoxide was determined by non-dispersive infrared spectroscopy. *Carbonyl compounds* (T-104): formaldehyde, acetaldehyde, acrolein, acetone, propionaldehyde, crotonaldehyde, methyl ethyl ketone, and butyraldehyde, were trapped in acetonitrile as 2,4-dinitrophenylhydrazine derivatives and determined with high performance liquid chromatography (HPLC) with ultraviolet detection (Houlgate et al, 1989). *Volatile organic compounds* (VOCs) (T-116): 1,3-butadiene, isoprene, acrylonitrile, benzene, and toluene were trapped in methanol-containing cold traps and analyzed by chromatography / mass spectrometry (GC/MS) (Byrd et al, 1990; Brunnemann et al, 1990). *Ammonia* (T-101), collected on both the pad and in sulfuric acid-containing impinger traps, was determined with ion exchange chromatography (Nanni et al 1990). *Hydrogen cyanide* (T-107), in particulate- and vapor-phase was determined colorimetrically after conversion to cyanogen chloride, reaction with pyridine, and complexation with diethyl acetone dicarboxylate (Collins et al, 1973; Rickert and Stockwell, 1979). *Nitrogen oxides* (T-110) were determined by chemiluminescence (Jenkins and Gill, 1980). *Aromatic amines* (T-102): 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, and 4-aminobiphenyl were determined by gas GC/MS from TPM extracted sequentially by hydrochloric acid and hexane, then

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derivatized with pentafluoropropionic acid anhydride and trimethyl amine (Pieraccini et al, 1992). *Benzo[a]pyrene* (T-103) was extracted from TPM with cyclohexane, concentrated, and analyzed by HPLC with fluorescence detection (Dumont and Larocque-Lazure, 1993). *Phenolic compounds* (T-114): hydroquinone, resorcinol, phenol, catechol, o-cresol, and (m+p)-cresol were extracted from TPM using acetic acid and analyzed by HPLC with fluorescence detection (Risner and Cash, 1990). *Pyridine, quinoline, and styrene* (T-112): the methanol-extract from TPM was combined with the collection in sequential methanol-containing cold traps and analyzed by GC/MS (White, et al, 1990). *Tobacco-specific nitrosamines* (TSNA) (T-111): N-nitrosonornicotine (NNN), 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanatabine (NAT) and N-nitrosoanabasine (NAB) were determined from TPM extracted with dichloromethane, fractionated through a basic alumina chromatography column, and analyzed by gas chromatography with thermal energy analysis detection (GC-TEA) (Fischer and Spiergelhalder, 1989). *Mercury* (T-108) was determined by collecting whole smoke in acidified potassium permanganate solution, followed by microwave digestion, and analysis by cold vapor atomic absorption (AA) spectroscopy (Van Delft and Vos, 1988). *Trace metals* (T-109): nickel, lead, cadmium, chromium, arsenic, and selenium were determined by electrostatic precipitation of smoke particulate phase, methanol extraction, microwave digestion with nitric and hydrochloric acids and hydrogen peroxide, and analysis by flameless (graphite furnace) AA spectroscopy. *Smoke "pH"* (T-113) was determined using a modified combination electrode positioned in the smoke collection path (Sensabaugh and Cardiff, 1967; Brunnemann and Hoffmann, 1974).

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Tobacco Blend Analyses

Tobacco blend analysis method details are available through the same sources given above for smoke constituent methods. *Tobacco nitrate* (T-308) was determined from acetic acid tobacco-extractions. Extracts were analyzed colorimetrically through reaction and complexation with hydrazine and copper (basic pH), sulfamilamide, and N-(1-napthyl)-ethylenediamine. *TNSA* (T-309): NNK, NNN, NAB, NAT were determined from ascorbic acid and dichloromethane extractions, with subsequent chromatography fractionation, using GC-TEA.

Statistics

To develop meaningful functional relationships for smoke constituents, cigarette brands in the exploratory sample set were selected to be representative of the market range. The design features of these brands established the boundary conditions for predictions of yields in other brands. The ranges of these features are summarized in Table 1. Mainstream tar, nicotine, and carbon monoxide yields at ISO machine-smoking conditions were investigated as potential independent variables for functional relationships.

The relationships between mainstream smoke tar, nicotine, or carbon monoxide and individual smoke constituents were developed and assessed using SAS® statistical software (Release 8.01, SAS Institute, Cary, NC.) and EXCEL® 97 (Microsoft©, Redmond, WA). The coefficients of determination, R^2, together with other diagnostic parameters were used to assess the strength and statistical significance of functional relationships. Diagnostic parameters included root mean square errors, predicted residual error sum of squares, and coefficient p-values.

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Functional relationships were gauged for their capacity to predict the smoke constituent yields of the validation-brand set by the magnitude of prediction errors (PE). These are the differences between predicted and measured smoke constituent yields. Prediction intervals (95% confidence level) were calculated for each set of constituent data for the exploratory brands. The intervals subsequently served as forecasting ranges for mainstream smoke constituent yields for another cigarette brand from a similar population of brands, e.g., the validation brands in this study.

RESULTS

Mainstream ISO Smoke Constituent Yields

Average mainstream tar, nicotine, carbon monoxide and smoke constituent yields for each brand in this study and the 1R4F reference cigarette are reported in Appendix 1. Measurement standard deviations are included. The results are grouped by exploratory-brand (codes E1-E39) and validation-brand (codes V1-V9) sample sets. Four of the brands contained primarily bright (flue-cured) tobaccos: codes E12, E31, V2, and V7. All others contained blended tobaccos. Several smoke constituent yields, particularly for lower tar-yield brands, were below the limit of detection (LOD) or limit of quantification (LOQ) established by the contract laboratory. These constituents, their respective LODs and LOQs, and number of brands with yields below quantitation levels are listed in Table 2.

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Table 2. Brand count with ISO smoke yields below quantitation levels

Smoke constituent	LOD	LOQ	number of brands below levels of: LOD	LOQ
selenium (ng/cig)	2.21	7.37	48	-
nickel (ng/cig)	6.47	21.6	46	2
chromium (ng/cig)	5.94	19.8	37	11
arsenic (ng/cig)	1.13	3.75	8	37
lead (ng/cig)	3.85	12.8	4	19
resorcinol (µg/cig)	0.158	0.526	3	11
crotonaldehyde (µg/cig)	0.980	3.29	1	12
mercury (ng/cig)	1.10	1.50	3	5
phenol (µg/cig)	0.573	1.91	2	5
o-cresol (µg/cig)	0.074	0.245	-	3
NAB (ng/cig)	0.634	2.00	-	2
quinoline (µg/cig)	0.007	0.024	-	1
m & p-cresols (µg/cig)	0.153	0.509	-	2
acrylonitrile (µg/cig)	0.282	0.939	-	2
toluene (µg/cig)	2.50	8.32	-	2
butyraldehyde (µg/cig)	0.810	2.70	-	1
ammonia (µg/cig)	0.725	2.45	-	1
acrolein (µg/cig)	0.710	2.37	-	1
propionaldehyde (µg/cig)	1.00	3.33	-	1
methyl ethyl ketone (µg/cig)	1.09	3.66	-	1
NNK (ng/cig)	3.72	12.4	-	1
pyridine (µg/cig)	0.237	0.791	-	1
styrene (µg/cig)	0.170	0.560	-	1

LOD = limit of detection, LOQ = limit of quantitation

Functional Relationships

(1) Regression Analysis

Functional relationships for each smoke constituent were generated through regression of the mean yields of the thirty-nine exploratory brands with their mean yields of tar, nicotine, or carbon monoxide, as measured at ISO smoking conditions. Analytical limits for LOQ and LOD were used instead of omitting brands from the analyses.

One of the basic assumptions for regression is that residuals are randomly distributed over the range of the independent variable (Kohler, 1994). However, for many of the smoke constituents, residuals tended to increase with increasing tar,

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nicotine, or carbon monoxide yield. This indicated that these constituents failed to meet the regression criterion for homogeneous and normally-distributed variance.

Weighted least squares (WLS) regression was used to stabilize the variances. The weighting factor used for this study was the inverse of the independent variable, e.g., 1/tar or 1/CO. The weighting factor was generally proportional to the constituent variances. Weighting resulted in randomly-distributed residuals, increased coefficients of determination, R^2, and lower root mean square errors and predicted residual error sum of squares compared to the unweighted analysis. Descriptions of weighted least squares regression and equations for prediction interval calculation are available in standard statitstics texts, including Kleinbaum (1988), Myers (1990), Glantz et al (1990), and Ott and Longnecker (2001).

(2) Correlation Strength

Mainstream tar, nicotine, and carbon monoxide were strongly correlated with each other and with most other mainstream constituents, as indicated by R^2. There were exceptions, however. The yields of nitric oxide, nitrogen oxides, and TSNAs were only weakly correlated ($R^2 < 0.80$) with tar, nicotine, or CO, but the correlations were improved by accounting for their precursors in tobacco. Smoke "pH" was relatively constant among brands, which resulted in very weak correlations ($R^2 < 0.30$). Similar findings for smoke "pH" had been reported in other studies (Massachusetts, 1999, 2000, 2001).

Smoke constituents tend to be associated more with either the particulate phase or the vapor phase of smoke. The distinction is not absolute because many constituents exist in both phases (Hoffmann, 1993). Nicotine, polycyclic aromatic hydrocarbons

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(PAHs), and TSNAs are examples of constituents associated primarily with the particulate phase (Wartman et al, 1959). Lower molecular-weight hydrocarbons such as benzene, butadiene, and toluene are primarily vapor-phase constituents. Hydrogen cyanide (Collins, et al, 1970) and ammonia (Sloan and Morie, 1974; Brunnemann and Hoffmann, 1975; Nanni, et al, 1990) have been found in both phases. The aldehydes and ketones monitored in this study reside primarily in the vapor phase, with the exception of formaldehyde which correlates highly with the particulate phase of smoke. The significant amount of formaldehyde retained by the Cambridge filter has been attributed to its hydrophilic nature and subsequent association with total particulate matter on the pad (Spencer and Chard, 1971).

Regression statistics were compared when tar, nicotine, or carbon monoxide was the independent variable. Generally, tar demonstrated the highest correlation with the smoke constituents. Carbon monoxide or nicotine would also be appropriate regressors for describing the yield relationships for smoke constituents as both nicotine and carbon monoxide yields were highly correlated with tar yields. Exploratory-brand average yields, simple weighted-least-squares-regression best-fit lines, 95% prediction intervals, and validation-brand average yields for each of the forty-two smoke constituents measured are shown in Figure 1. To exemplify the measurement variability, one-standard-deviation error bars are included for several constituents. Standard deviation data for all of the constituents are included in Appendix 1. All regressions were statistically significant at the 95% confidence level and regression coefficients were statistically different from zero.

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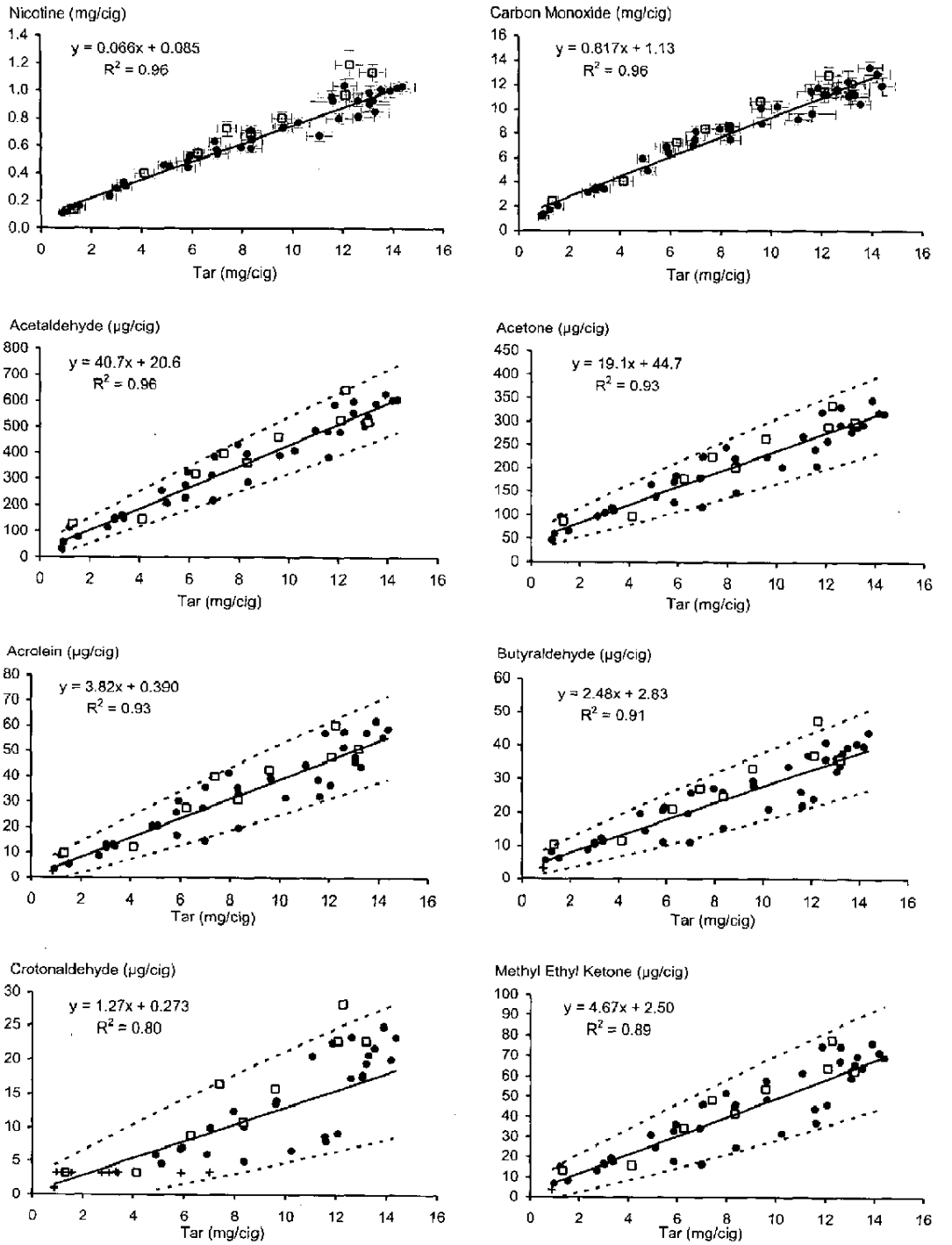
Figure 1: Plots of ISO-method constituent yield vs tar yield from weighted (1/tar) linear regression
(—) Best fit regression equation, (- - -) 95% Prediction interval, ● Exploratory brands, □ Validation brands, + not quantitated



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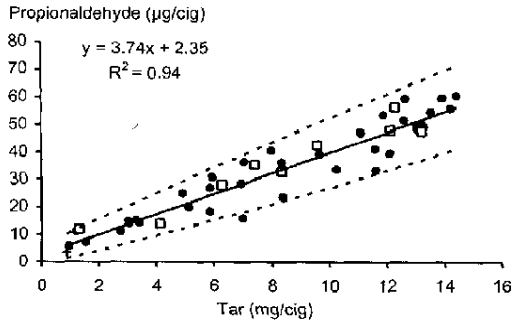

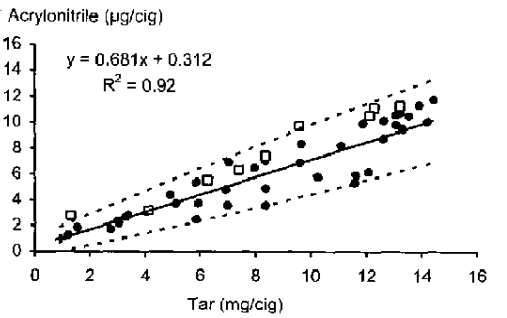

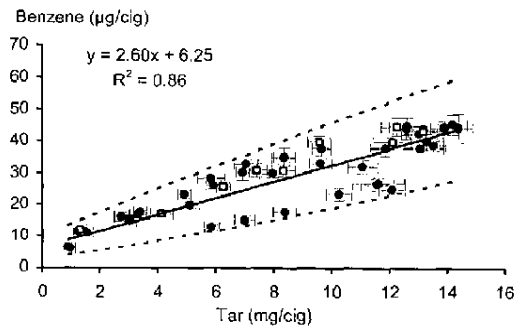

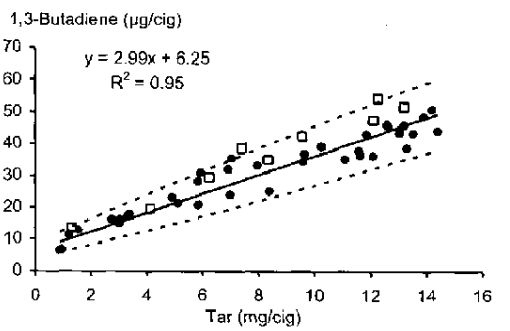

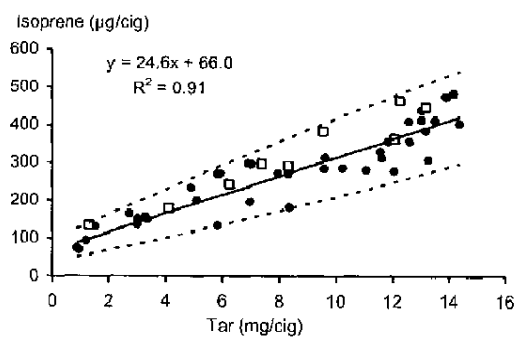

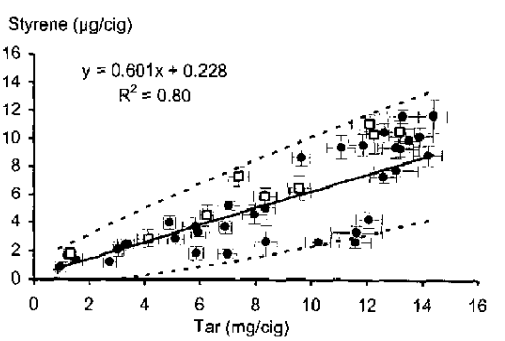

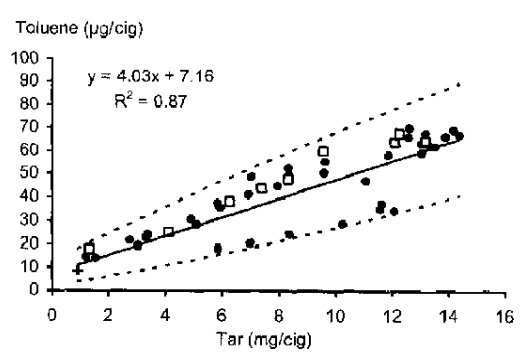

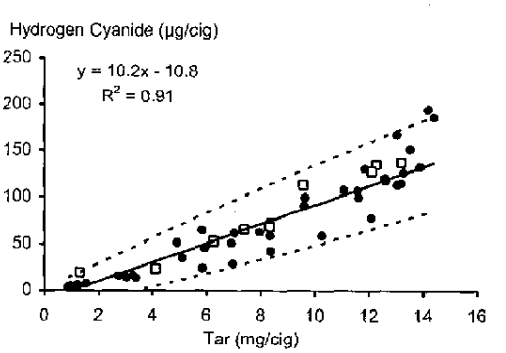

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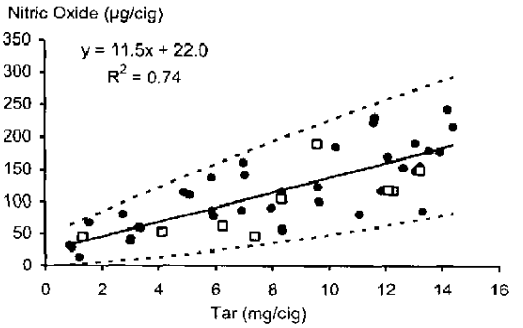
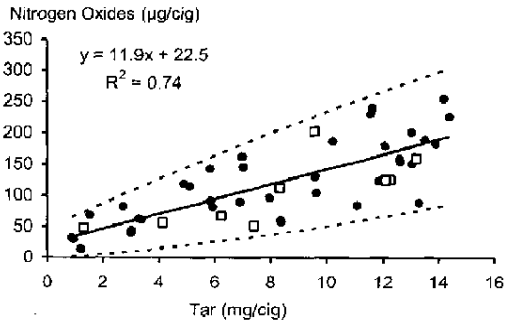
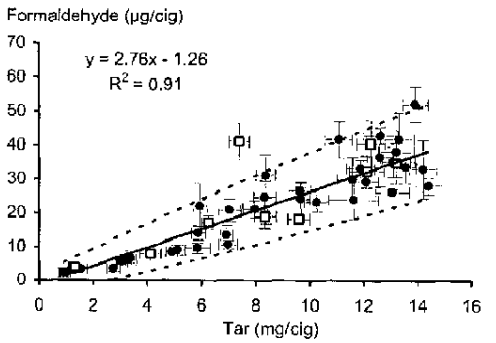
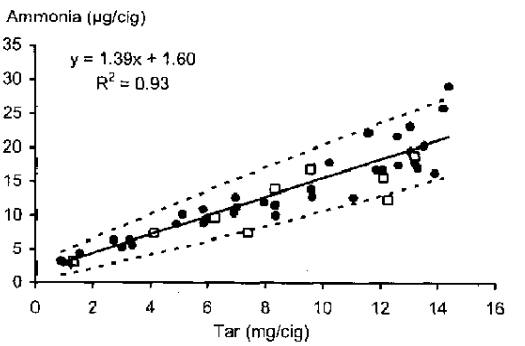
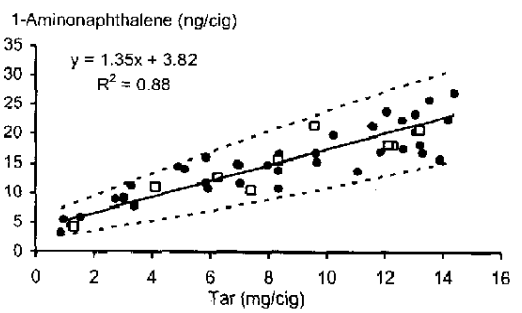
Figure 1: Plots of ISO-method constituent yield vs tar yield from weighted (1/tar) linear regression
(—) Best fit regression equation, (- - -) 95% Prediction interval, • Exploratory brands, □ Validation brands, + not quantitated

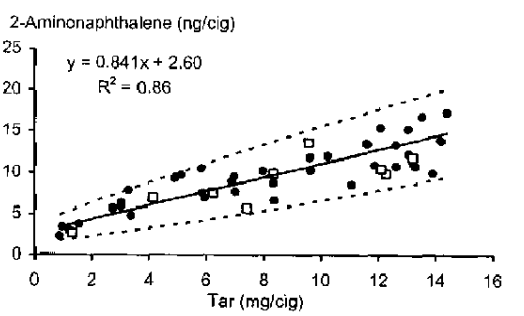


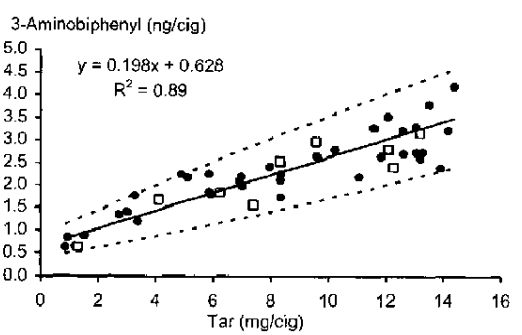












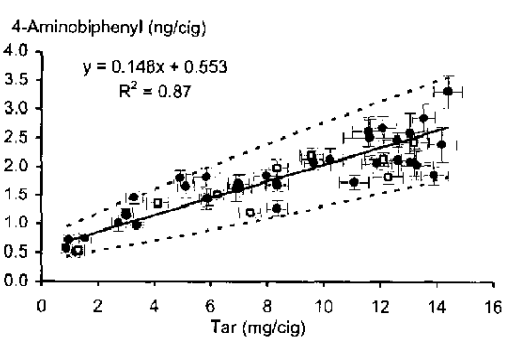


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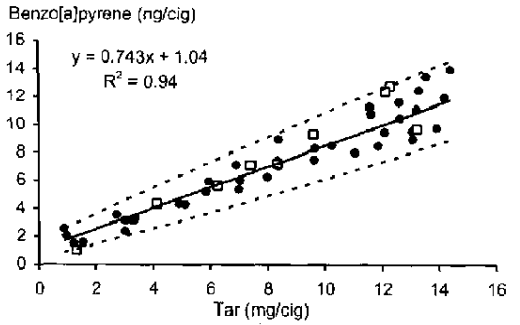
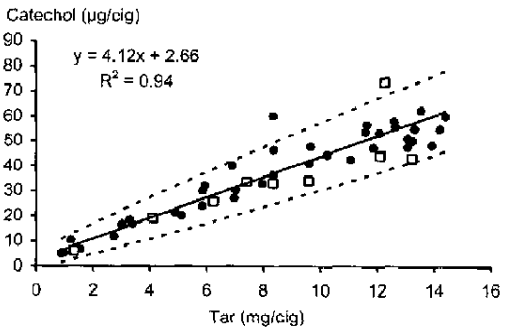
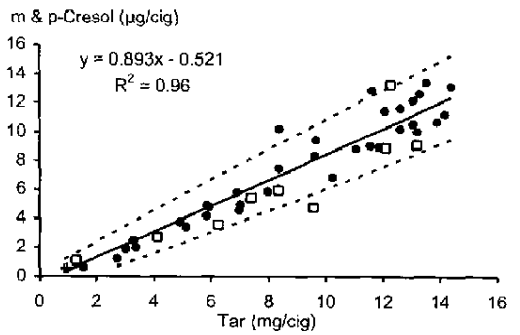
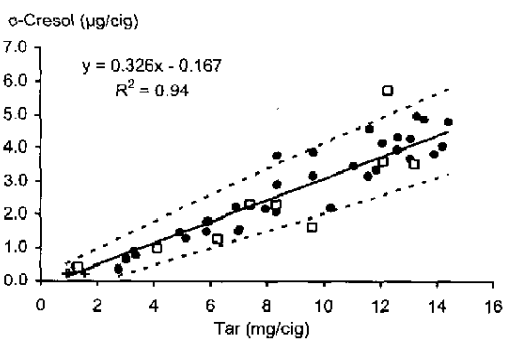
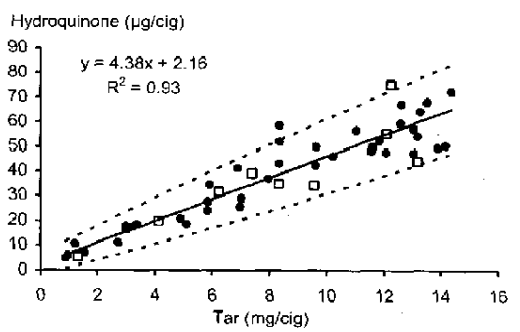
Figure 1: Plots of ISO-method constituent yield vs tar yield from weighted (1/tar) linear regression
(—) Best fit regression equation, (- - -) 95% Prediction interval, • Exploratory brands, □ Validation brands, + not quantitated

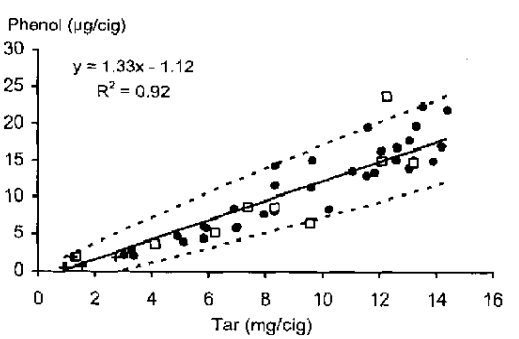


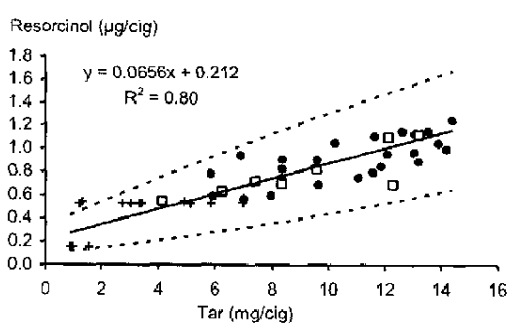


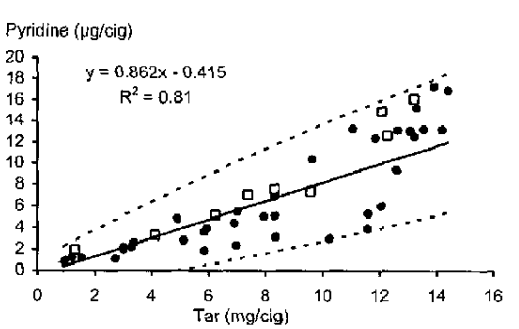












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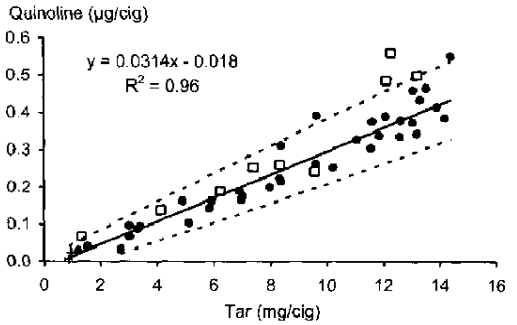
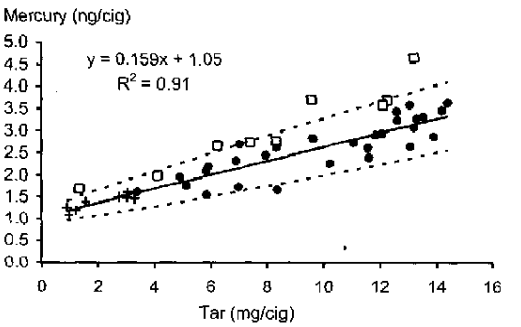
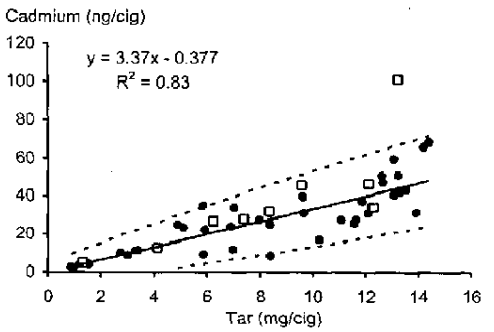
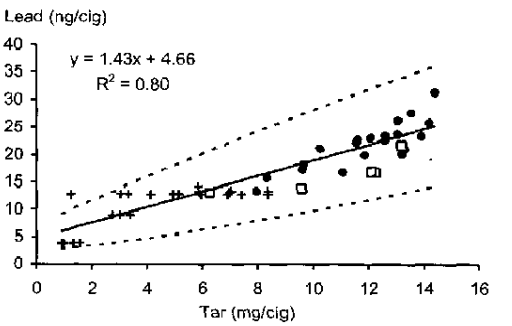
Source: https://www.industrydocuments.ucsf.edu/docs/rhlx0001

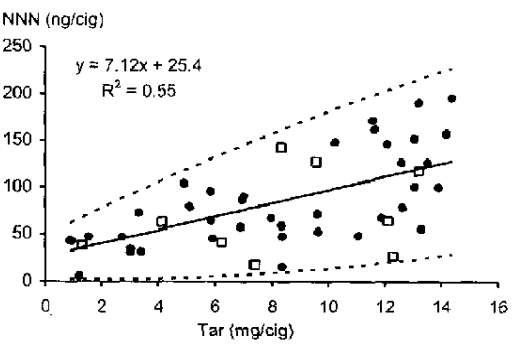
Figure 1: Plots of ISO-method constituent yield vs tar yield from weighted (1/tar) linear regression
(—) Best fit regression equation, (- - -) 95% Prediction interval, • Exploratory brands, □ Validation brands, + not quantitated

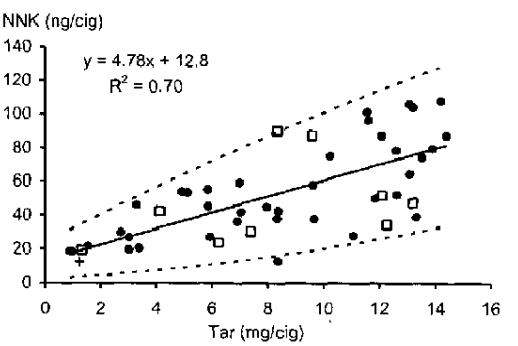


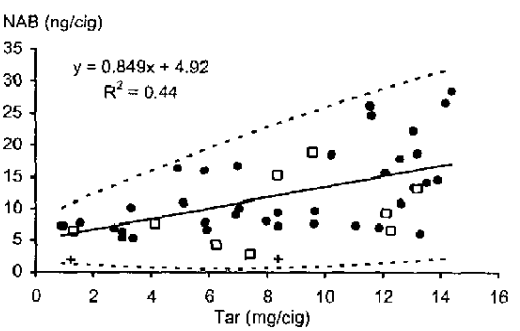


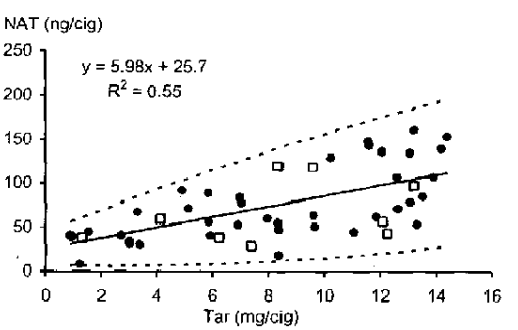












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(3) Mainstream TSNA and Nitrogen Oxides Treatment

Many of the chemical constituents found in smoke are generated during combustion from precursors found in the leaf: phenolic compounds are derived partially from cellulosic materials in leaf; some nitrogenous compounds are derived partially from proteins in leaf; and nitrogen oxides are derived partially from nitrates in leaf (Baker, 1999). The amounts of these constituents found in mainstream smoke depend in part on the amounts of their precursors in the tobacco that is consumed during puffing and the conversion efficiencies of the precursors.

Other smoke constituents are distilled intact from the tobacco during the smoking process. Constituents such as nicotine (Rustemeier and Piadé, 1999) and, to some extent, TSNAs (Fischer et al, 1990) are in this category. The amounts of these constituents found in mainstream smoke are functions of their concentrations in the tobacco itself and their transfer efficiencies to smoke during puffing.

Nitrogen oxides and TSNA deliveries weakly correlated with tar deliveries. These results are not unexpected since cigarettes of similar construction will have similar tar deliveries, but their tobacco blends can have widely different nitrate and TSNA levels. Therefore, the deliveries of these constituents in smoke will depend on both cigarette construction and the amount of precursors or source concentration in the blends.

Tobacco-blend nitrate and TSNA concentrations were used to modify functional relationships for predicting the yields of nitrogen oxides and TSNAs in smoke. Tobacco blend concentrations of nitrate and TSNAs for each brand style in this study are found in Appendix 2.

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Source: https://www.industrydocuments.ucsf.edu/docs/rhlx0001

For TSNA smoke yields, multiple regressions using tar and cigarette tobacco-blend TSNA levels were assessed. The amount of the TSNA in the tobacco blend of each cigarette type was calculated from the cigarette tobacco weight and the weight-percentages of the TSNA in the blend. Multiple regression relationships for NNN, NNK, and NAT were significantly improved by this inclusion over simple linear regression models, as evidenced by higher respective R^2 values, lower root mean square errors, and lower prediction errors for both the exploratory and validation brands. NAB relationship improvement was marginal.

Even with an overall improvement from multiple regression, smoke TSNA yield prediction errors tended to be greater for brands at the low or high range of tar yield or tobacco TSNA content. For this reason, variable transformation techniques were employed. Of the transformations investigated, the square root of the product of tar-yield and cigarette blend-TSNA concentration gave the best result. The relationship used for prediction was a linear regression of smoke TSNA yields with the interactive variable [sqrt (tar $\times$ cigarette blend-TSNA)]. Residuals from this regression were homogeneously and normally distributed over the transformed variable range. The result was a significant increase in regression quality with higher R^2 and lower prediction errors for all of the brands in the validation set. This model also allowed for one-dimensional prediction intervals and simpler visualization. NAB was an exception, however. The qualities of the two prediction models, one based on multiple regression using tar and cigarette blend-NAB concentration and one based on a square root-transformed interactive variable with tar and cigarette blend-NAB concentration, were similar. Of the four TSNAs analyzed, prediction errors were relatively greater for NAB.

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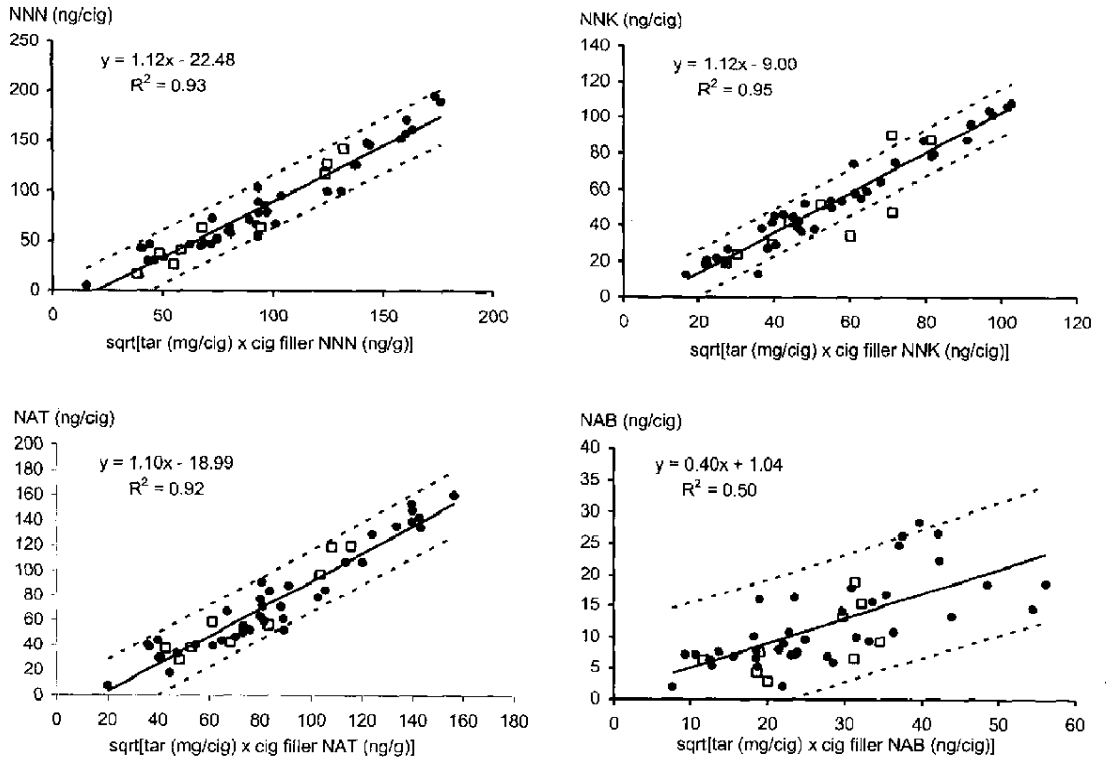
Source: https://www.industrydocuments.ucsf.edu/docs/rhlx0001

Figure 2 contains transformed variable regression models and prediction intervals for mainstream smoke NNN, NNK, NAT, and NAB yields.

Figure 2: Prediction models for ISO mainstream tobacco specific nitrosamine yields
(—) Best fit regression equation, (- - -) 95% Prediction interval, ● Exploratory brands, □ Validation brands



A similar approach was employed in regressing nitric oxide and nitrogen oxides yields using [sqrt (tar × cigarette blend-nitrate)] as the independent variable. Prediction models for nitric oxide and nitrogen oxides are found in Figure 3.

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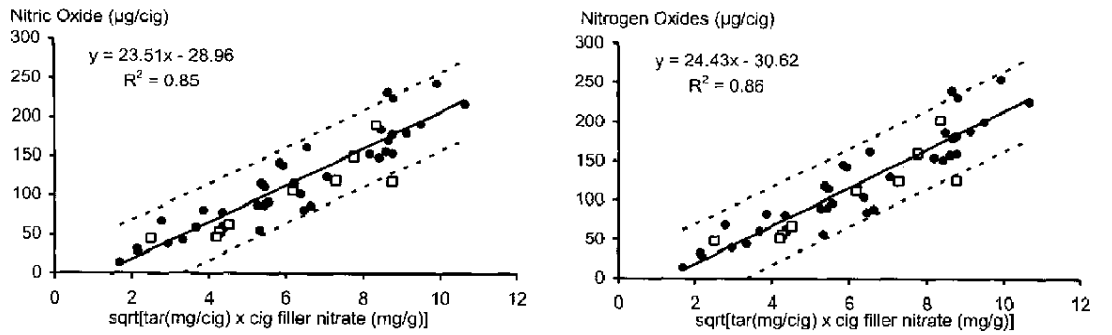
Source: https://www.industrydocuments.ucsf.edu/docs/rhlx0001

Figure 3: Prediction models for ISO mainstream nitrogen oxides yields
(—) Best fit regression equation, (- - -) 95% Prediction interval, • Exploratory brands, □ Validation brands



With these transformed interactive variables, mainstream smoke TSNA and nitric oxide(s) predicted smoke yields were improved relative to those of simple linear regressions where tar was the only independent variable. The use of prediction models beyond simple linear regression for TSNA or nitrogen oxides yields would have less impact if all brands were similar in tobacco blend-nitrate or blend-TSNA concentration. Since this study included brands from a wide range of regional markets, and consequently a wide range of concentrations of these tobacco components, different regression models were warranted.

(4) Prediction Error

To test the reliability of the regression equations, the measured constituent yields for the nine validation brands were compared with the predicted yields and the 95% prediction intervals. Table 3 includes the predicted smoke yields and calculated prediction errors (PE). A positive or negative PE indicates the predicted yield was greater or less, respectively, than the average measured yield. Greater than 90% of constituent yields for the validation brands were within the 95% prediction intervals and prediction errors were similar in magnitude to measurement standard deviations. Measured brand-average constituent yields outside the prediction intervals are

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Source: https://www.industrydocuments.ucsf.edu/docs/rhlx0001

underlined in Table 3. No particular constituents were consistently outside of the prediction intervals across the validation brands. Two validation brands contained primarily flue-cured tobacco blends. One brand, code V2, was outside the prediction intervals for smoke ammonia (over-predicted) and for catechol, cresols, phenol, and hydroquinone (under-predicted). This was consistent with general findings for flue-cured tobaccos (Griest and Guerin, 1977). A second all-flue-cured brand, code V7, was over-predicted for ammonia yield and under-predicted for formaldehyde yield. Its catechol, phenol, and hydroquinone yields, however, were within the range for blended brands. The tobacco-specific nitrosamine, NNN, was considerably lower for these two brands and the two exploratory all-flue-cured brands, codes E12 and E31, compared to blended brands. This is also consistent for flue-cured tobaccos. The apparent inconsistency in relative phenolic constituent yields for these flue-cured brands may be due to regional growing conditions and curing practices, tobacco grades, or tobacco varieties in each brand. As noted by Griest and Guerin, these differences can have a greater impact on smoke chemistry than differences due to tobacco type.

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Source: https://www.industrydocuments.ucsf.edu/docs/rhlx0001

Table 3. Smoke constituent predicted ISO-method yields and prediction errors for validation brands (V1-V9) using simple linear or transformed-interactive-variable regression

	V1		V2		V3		V4		V5		V6		V7		V8		V9	
Smoke Constituents	Predicted	PE[3]	Predicted	PE[3]	Predicted	PE[3]	Predicted	PE[3]	Predicted	PE[3]	Predicted	PE[3]	Predicted	PE[3]	Predicted	PE[3]	Predicted	PE[3]
acetaldehyde (µg/cig)[1]	361	-2	521	-121	276	-43	189	43	75	-54	411	-50	323	-73	559	39	515	-12
acetone (µg/cig)[1]	204	3	279	-56	164	-12	124	27	70	-17	227	-34	186	-38	297	-2	276	-12
acrolein (µg/cig)[1]	32.2	1.4	47.2	-13.1	24.3	-3.3	16.2	4.1	5.4	-4.3	37.0	-5.6	28.7	-11.2	50.8	0.0	46.6	-1.1
butyraldehyde (µg/cig)[1]	23.5	-1.2	33.3	-14.2	18.4	-2.6	13.1	1.7	6.1	-4.1	26.6	-6.5	21.2	-5.8	35.6	-0.1	32.9	-4.1
crotonaldehyde (µg/cig)[1]	10.9	0.0	15.9	-12.4	8.2	-0.6	5.5	2.2	3.3	0.0	12.4	-3.4	9.7	-6.8	17.0	-5.8	15.7	-7.2
methyl ethyl ketone (µg/cig)[1]	41.4	-0.3	59.8	-18.2	31.7	-2.8	21.8	5.9	8.7	-4.7	47.2	-6.7	37.1	-11.3	64.1	1.3	59.0	-5.2
propionaldehyde (µg/cig)[1]	33.5	0.7	48.2	-8.2	25.7	-2.4	17.8	4.0	7.3	-4.6	38.1	-4.4	30.0	-5.4	51.7	3.9	47.6	-0.4
acrylonitrile (µg/cig)[1]	6.0	-1.4	8.7	-2.5	4.6	-0.9	3.1	-0.1	1.2	-1.6	6.8	-2.9	5.4	-1.0	9.3	-2.0	8.6	-2.0
benzene (µg/cig)[1]	27.9	-2.8	38.1	-6.3	22.5	-2.9	17.0	0.0	9.7	-2.3	31.1	-8.5	25.5	-5.3	40.5	-2.6	37.7	-1.9
1,3-butadiene (µg/cig)[1]	31.2	-3.8	42.9	-11.2	24.9	-4.4	18.6	-0.8	10.2	-3.3	34.9	-7.5	28.4	-10.4	45.7	-5.9	42.4	-5.0
isoprene (µg/cig)[1]	272	-19	368	-98	220	-24	168	-11	99	-36	302	-81	248	-48	391	-57	364	0
styrene (µg/cig)[1]	5.2	-0.7	7.6	-2.8	4.0	-0.6	2.7	-0.2	1.0	-0.8	6.0	-0.5	4.7	-2.6	8.2	-2.4	7.5	-3.6
toluene (µg/cig)[1]	40.7	-7.0	56.6	-10.9	32.3	-5.9	23.8	-1.2	12.5	-5.3	45.7	-14.3	37.0	-6.8	60.3	-4.1	55.9	-7.7
hydrogen cyanide (µg/cig)[1]	74.3	6.0	114.4	-20.4	53.0	0.2	31.4	8.0	2.7	-16.7	87.0	-25.9	64.7	-0.7	123.9	-13.2	112.7	-15.0
nitric oxide (µg/cig)[2]	116	11	177	60	77	15	71	18	30	-15	167	-23	70	23	153	4	143	24
nitrogen oxides (µg/cig)[2]	120	8	184	58	80	13	74	17	31	-18	173	-29	72	21	159	-1	148	23
mercury (ng/cig)[1]	2.4	-0.4	3.0	-0.7	2.0	-0.6	1.7	-0.3	1.3	-0.4	2.6	-1.1	2.2	-0.5	3.1	-1.5	3.0	-0.6
formaldehyde (µg/cig)[1]	21.8	2.7	32.6	-8.0	16.0	-1.3	10.2	2.2	2.4	-1.6	25.2	7.0	19.2	-22.0	35.2	0.4	32.2	-0.2
ammonia (µg/cig)[1]	13.2	-0.8	18.7	6.3	10.3	0.6	7.4	0.0	3.4	0.3	15.0	-2.0	11.9	4.4	20.0	1.1	18.5	2.8
1-aminonaphthalene (ng/cig)[1]	15.1	-0.5	20.4	2.3	12.3	-0.4	9.4	-1.6	5.6	1.3	16.8	-4.7	13.8	3.3	21.7	1.0	20.2	2.0
2-aminonaphthalene (ng/cig)[1]	9.6	-0.2	12.9	3.1	7.9	0.3	6.1	-0.8	3.7	1.1	10.7	-2.9	8.8	3.2	13.7	1.9	12.8	2.4
3-aminobiphenyl (ng/cig)[1]	2.28	-0.24	3.06	0.66	1.87	0.03	1.45	-0.23	0.89	0.26	2.53	-0.44	2.09	0.54	3.24	0.08	3.03	0.24
4-aminobiphenyl (ng/cig)[1]	1.79	-0.19	2.37	0.55	1.48	-0.03	1.17	-0.19	0.75	0.21	1.97	-0.23	1.65	0.45	2.51	0.08	2.35	0.22
benzo[a]pyrene (ng/cig)[1]	7.23	0.01	10.15	-2.61	5.68	0.08	4.11	-0.20	2.02	1.00	8.15	-1.13	6.54	-0.60	10.84	1.17	10.03	-2.33
catechol (µg/cig)[1]	37.0	3.8	53.1	-20.3	28.4	2.5	19.7	0.3	8.1	2.0	42.1	7.9	33.1	-0.7	57.0	13.9	52.5	8.3
m & p-cresols (µg/cig)[1]	6.9	1.0	10.4	-2.8	5.1	1.5	3.2	0.5	0.7	-0.4	8.0	3.3	6.1	0.7	11.3	2.2	10.3	1.4
o-cresol (µg/cig)[1]	2.55	0.25	3.83	-1.91	1.87	0.58	1.18	0.19	0.26	-0.13	2.96	1.32	2.25	-0.06	4.13	0.59	3.78	0.17
hydroquinone (µg/cig)[1]	38.7	3.7	55.9	-19.2	29.5	-1.9	20.2	0.6	7.9	2.4	44.1	9.9	34.6	-4.6	60.0	16.0	55.2	-0.2
phenol (µg/cig)[1]	10.0	1.3	15.2	-8.6	7.2	2.0	4.4	0.7	1.9	0.0	11.6	5.1	8.7	0.0	16.4	1.7	15.0	0.0
resorcinol (µg/cig)[1]	0.76	0.06	1.02	0.33	0.62	-0.01	0.48	-0.06	0.53	0.00	0.84	0.02	0.70	-0.02	1.08	-0.04	1.01	-0.09
pyridine (µg/cig)[1]	6.8	-0.8	10.2	-2.5	5.0	-0.2	3.1	-0.2	0.7	-1.2	7.8	0.4	6.0	-1.1	11.0	-5.2	10.0	-4.9
quinoline (µg/cig)[1]	0.24	-0.02	0.37	-0.19	0.18	-0.01	0.11	-0.03	0.02	-0.04	0.28	0.04	0.21	-0.04	0.40	-0.10	0.36	-0.12
NNN (ng/cig)[2]	124.7	-17.6	39.0	12.4	42.7	1.5	53.2	-9.5	31.6	-6.4	116.4	-10.5	20.4	3.4	115.5	-1.2	83.0	19.5
NNK (ng/cig)[2]	70.5	-19.6	58.3	24.0	24.9	1.2	40.2	-2.0	21.6	2.4	82.0	-5.4	35.2	5.2	70.8	23.5	49.4	-2.3
NAT (ng/cig)[2]	108.9	-11.1	56.6	13.9	39.9	1.5	48.6	-10.3	28.5	-9.3	100.5	-18.1	34.6	6.0	95.2	2.0	73.1	16.8
NAB (ng/cig)[2]	13.9	-1.5	13.4	6.9	8.4	4.2	8.6	1.0	5.7	-0.8	13.5	-5.4	9.0	6.2	12.9	-0.3	14.8	5.6
cadmium (ng/cig)[1]	27.7	-4.5	40.9	6.7	20.7	-6.1	13.5	0.5	4.1	-1.1	31.9	-13.7	24.6	-3.5	44.1	-56.9	40.4	-6.0
lead (ng/cig)[1]	16.6	3.8	22.2	5.5	13.6	0.6	12.8	0.0	3.9	0.0	18.3	4.5	15.2	2.4	23.5	1.8	22.0	5.1

[1]Weighted least squares regression. [2]Transformed variable regression (see figures 2 and 3). [3]Prediction error (PE) = predicted yield - measured yield. Yields outside of the 95% predicted interval are underlined. When predicted yield < LOQ and > LOD, LOQ is reported. When predicted yield < LOD, LOD is reported.

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Tobaccos from different regions will be impacted by agricultural practices and growing conditions. For example, the concentration of metals in tobacco, and consequently smoke, is affected by agricultural practices and growing conditions (Stohs et al, 1997; Smith et al, 1997). Smoke cadmium yield for brand V8, at the time of this study, was beyond the prediction interval. This could be the result of unusual growing conditions for a particular crop year or years. Although tobacco blending over several crop years tends to mitigate year-to-year differences, any uncharacteristic change in yield would not be predicted in a benchmark study.

One underlying premise of benchmarking is that brands are consistent over a relevant time period. Swauger et al (2002) compared smoke constituent yields for a broad sampling of U.S. commercial cigarette brands in 1995, 1998, and 2000. Among their findings was smoke constituent yields of commercial U.S. cigarettes had remained fairly constant between 1995 and 2000. Currently, tobacco curing in the U.S. is undergoing a transition for the purpose of reducing tobacco-specific nitrosamines in flue-cured tobacco (Fisher, 2000). The benchmarking results reported here for TSNAs will therefore need revision as tobaccos cured with modified techniques are blended into cigarette products for the U.S. market or for export from the U.S.

(5) Alternative When Brands Contain Carbon in Filter Design

Nine brands in the exploratory group contained carbon in their filter construction. It is well known that carbon, i.e., activated charcoal, has the potential to selectively adsorb many vapor-phase constituents from mainstream smoke (Baggett and Morie, 1975; Williamson et al, 1965). Carbon monoxide and oxides of nitrogen are generally not affected by carbon (Tiggelbeck, 1972). Brands with carbon-containing filters would be

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expected to influence the functional regression relationships of vapor-phase constituents with a bias toward lower predicted yields for non-carbon filter brands. Similarly, some vapor-phase constituents would be over-predicted for brands with filters containing carbon. This influence was reflected in both the quality of the regression relationships (regression diagnostic statistics) and prediction interval width.

Functional relationship models for vapor-phase constituents were consequently expanded to include a factor for the presence of carbon in filters. Multiple regression relationships were developed using tar and an "indicator" variable of 1 or 0 for the presence or absence of carbon, respectively, for the thirty-nine exploratory brands. Again, regressions were weighted with the inverse of tar yield. The results showed general, though moderate, reductions in root mean square errors and increases in R^2 for most of the vapor-phase constituents. Use of an "indicator" variable for filters with carbon does not take into account different filter constructions, different weights of carbon in those filters, or surface areas and activities of carbons used in various brands. Multiple regression adds a level of complexity to both relationship development and application of those relationships to predicting yields of other brands. The potential impact of carbon filters should be considered in assessing brand constituent yields and predicting relationships for vapor-phase constituents. The benchmarking approach would be equally valid if brands with carbon in filters were modeled separately from those without carbon in filters. It is noted that Figure 1 contains only the results for simple weighted regression and not multiple regression.

(6) Relative Prediction Errors

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To capture the overall impact of the different regression models on prediction errors for the validation brands, an average absolute relative prediction error (average ARPE) was calculated for each constituent. The relative prediction error for a validation brand's constituent yield is the difference in measured and predicted yields divided by the measured yield. The constituent average ARPE was simply the sum of absolute relative prediction errors for each brand averaged over the nine validation brands. The average ARPE was compared to the coefficient of variation (%CV) for each constituent averaged over the nine validation brands. These averaged values are found in Table 4. For vapor- and particulate-phase constituents, prediction errors were generally within two standard deviations of the measured yield. Average ARPE's were therefore approximately two times the respective average %CV. For smoke constituents measured at microgram and nanogram levels, small differences in predicted and measured yields can result in large ARPE's. For example, the average ARPE for the nine brands for phenol and pyridine were 22% and 21%, respectively. Those percentages would equate to average prediction errors of 2.1 micrograms and 1.8 micrograms. An ARPE of 21% for NNK yields would equate to an average prediction error of 10 nanograms. Similarly, if the average predicted error for 4-aminobiphenyl had been only 1.0 nanogram, the ARPE would be 50%. The calculated ARPE for 1-aminobiphenyl in this study was 17%.

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Table 4. Average measured yield coefficients of variation (%CV) and absolute relative prediction errors for validation brands V1-V9

Smoke constituent	Average %CV [2]	Average ARPE [1]: Simple with tar (weighted)	Multiple: tar and carbon factor (weighted)	Simple with (tar x filler NO_3)$^{0.5}$	Smoke constituent	Average %CV [2]	Average ARPE [1]: Simple with tar (weighted)	Simple with (tar x filler TSNA)$^{0.5}$
acetaldehyde	10%	16%	15%	-	formaldehyde	15%	22%	-
acetone	8%	12%	11%	-	ammonia	8%	19%	-
acrolein	11%	18%	17%	-	1-aminonaphthalene	14%	15%	-
butyraldehyde	11%	17%	15%	-	2-aminonaphthalene	12%	23%	-
crotonaldehyde	13%	25%	25%	-	3-aminobiphenyl	8%	17%	-
methyl ethyl ketone	9%	17%	15%	-	4-aminobiphenyl	6%	17%	-
propionaldehyde	9%	14%	13%	-	benzo[a]pyrene	9%	20%	-
acrylonitrile	7%	22%	19%	-	catechol	7%	18%	-
benzene	5%	11%	7%	-	m & p-cresols	7%	29%	-
1,3-butadiene	6%	16%	13%	-	o-cresol	8%	27%	-
isoprene	6%	13%	10%	-	hydroquinone	7%	19%	-
styrene	13%	22%	16%	-	phenol	8%	22%	-
toluene	6%	15%	10%	-	resorcinol	7%	10%	-
hydrogen cyanide	9%	21%	21%	-	pyridine	14%	21%	-
mercury	9%	22%	19%	-	quinoline	9%	23%	-
nitric oxide	11%	na	na	26%	NNN	11%	na	17%
nitrogen oxides	10%	na	na	24%	NNK	14%	na	21%
					NAT	8%	na	17%
					NAB	16%	na	60%
					cadmium	10%	21%	-
					lead	21%	15%	-

(1) Absolute relative prediction error = ((absolute prediction error)/measured yield) x 100. (2) %CV = (measured yield standard deviation/mean measured yield) x 100.

DISCUSSION

A benchmarking approach for providing reliable smoking machine-generated cigarette smoke constituent yield information was evaluated with a worldwide sample of commercial brands. The approach was applied to mainstream smoke yield data obtained at standard ISO smoking conditions. Results for the diverse range of brands supported the underlying assumption that smoke constituent precursors in tobacco were available somewhat uniformly across tobacco blends from the different regions. Mainstream smoke constituent yields increased with increasing tar, nicotine, or carbon monoxide yields. Machine-generated smoke tar and constituent yields are directly related to the amount of tobacco consumed during puffing, which in turn is dependent on cigarette design.

The execution and utility of a benchmark study are based on several key elements:

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(1) *Test cigarette brands have design features representative of the marketplace of interest*. Selected brands encompass the variation in the market's cigarette design parameters, including tobacco blends, filter construction, ventilation, cigarette paper porosity, cigarette length and diameter, and processed tobacco components. Although this emphasis on 'differences' may result in weaker overall correlations due to wider brand design dispersion, the functional relationships and predictive intervals will be more generally applicable to predicting yields for other individual brands within the market. Brand differences, rather than similarities, were also emphasized in the 1999 Massachusetts Benchmark study (Borgerding, 2000).

(2) *Cigarettes for which smoke constituent yields will be predicted have design characteristics within the boundary established by benchmarking test brands selected.* There are two basic means of prediction in regression, i.e., interpolation and extrapolation. Interpolation is relatively robust in that predictions are made within the range of the data used to construct the functional relationships and prediction validity can be checked against actual observations. Extrapolation involves more risk because predictions are made beyond the range of original data. Regression model validity cannot be guaranteed beyond the defined boundaries (i.e., brand design features and tar range). This particular study is applicable to conventional lit-end Philip Morris brands manufactured in various regions and with design boundaries as defined in Table 1. Results from using these relationships to predict constituent yields of other brands for which brand design and quality are not known would be open to question. Additionally, these relationships would not be applicable to unique product designs, such as the Philip Morris Accord® or Oasis™ electrically heated cigarette smoking

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systems.

(3) *Brands are consistent over time*. For benchmarking functional relationships to be valid over some time frame, the brands on which those relationships were based need to be reasonably consistent in design, quality, and components within that time frame. Brand consistency does not ensure that measured constituent yields will not have variation, however. Any analytical measurement contains uncertainty. Sources and potential magnitude of these uncertainties, and their impact on generating and using functional relationships should be recognized. The utility of the benchmark approach is determined by how closely predicted yields compare to measured yields. Prediction errors for smoke constituents of the validation brands in this study were moderate when examined relative to other sources of potential variation. One source is the analytical variation for a particular cigarette brand sample, as evidenced by the magnitude of the smoke constituent analyses standard deviations. Variation can be due to minor differences within the sample or to normal variation in analytical methods. Testing laboratories practicing sound quality control procedures will minimize and quantitate, but not eliminate, analytical variation.

Variability in method execution over time was estimated by comparing average constituent yields for the 1R4F Kentucky reference cigarette reported by the contract lab for several company studies. Similar trends in measurement variation would be anticipated for other laboratories using internally-validated methods. Analyses were performed within an eleven-month period with the laboratory using the same methods throughout. Consistency of the reference cigarette was assumed. As seen in Table 5, part A, 95% confidence intervals for measured mean yields of standard smoke

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parameters (tar, nicotine, carbon monoxide) were 5% to 7%. For other mainstream smoke constituents, the 95% confidence intervals for the measured mean yields were considerably wider. Smoke constituent 95% confidence intervals ranged from 8% to approximately 50% (resorcinol and NAB being most variable), with an average of 20% for all constituents. These confidence intervals were similar in magnitude to prediction errors in the current benchmark study.

Another source of variation in smoke constituent yields can be the cigarette brand itself. Three potential sources of cigarette variability are described in Annex C of ISO Standard 8243 (1991). Short-term variability is attributed to minor fluctuations in tobacco blend, tobacco weight, or non-tobacco components (e.g., paper permeability, filter ventilation level) during manufacturing. Medium-term variability reflects short-term variability plus batch-to-batch changes in non-tobacco components, tobacco grades, and machinery performance. Long-term variability can include crop year differences or machinery replacement, for example, and are additive with short- and medium-term variability. As previously noted, natural products such as tobacco are subject to crop-year weather variations, regional agricultural practices, and tobacco processing differences. Tobacco blending from different crop years minimizes these differences, but some degree of medium- and long-term variation is expected. For this reason, a smoke constituent yield measured for a brand produced today could vary somewhat from the yield for the same brand produced at another time.

An example of typical smoke constituent yield variation for a single brand produced at different times is seen in Table 5, part B. Selected smoke constituents were analyzed over a nine-month period by a company research laboratory. The measured

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yield variation encompasses short- and medium-term brand variation and also inherent method variation. A significant point of the information in Table 5, part B, is the magnitude of the 95% confidence intervals around the mean smoke constituent yields. Again, tar, nicotine, and carbon monoxide variation was relatively low. The average of all 95% confidence intervals for other analyzed smoke constituents was +/- 25% of the means for this time period, with a range of 8% to 63%. Those with the larger confidence intervals tended to be constituents present in lower concentrations. These intervals are only moderately greater than the confidence intervals around the means for the 1R4F reference cigarette tested by the contract laboratory at various points in time. The intervals are also similar in magnitude to the average relative prediction errors for the validation brands in this current benchmark study.

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Table 5. Smoke constituent yield variation: (A) single production analyzed over time and (B) multiple productions at points-in-time

	(A) 1R4F reference cigarette (5 studies)					(B) Commercial brand (9 production samples)[2]				
Analysis	Average of means	Std error[1]	Upper 95% CI[1]	Lower 95% CI[1]	CI % of means average	Average of means	Std error[1]	Upper 95% CI[1]	Lower 95% CI[1]	CI % of means average
tar (mg/cig)	9.1	0.3	9.8	8.4	7%	6.1	0.2	6.5	5.8	6%
nicotine (mg/cig)	0.75	0.02	0.79	0.72	5%	0.53	0.01	0.55	0.51	4%
carbon monoxide (mg/cig)	11.9	0.3	12.5	11.3	5%	7.4	0.4	8.1	6.7	10%
acetaldehyde (µg/cig)	560	46	649	470	16%	428	38	503	353	18%
acetone (µg/cig)	296	13	320	271	8%	248	24	296	200	19%
acrolein (µg/cig)	47.0	5.7	58.1	35.8	24%	44.9	4.7	54.2	35.7	21%
butyraldehyde (µg/cig)	33.8	4.2	42.0	25.7	24%	30.5	3.5	37.3	23.8	22%
crotonaldehyde (µg/cig)	13.9	1.4	16.6	11.1	20%	9.8	1.9	13.5	6.1	38%
methyl ethyl ketone (µg/cig)	65.2	9.0	82.8	47.6	27%	52.3	4.7	61.6	43.1	18%
propionaldehyde (µg/cig)	50.1	3.6	57.2	42.9	14%	34.6	3.5	41.4	27.9	20%
acrylonitrile (µg/cig)	8.9	0.9	10.6	7.1	20%	8.5	2.3	13.0	4.0	53%
benzene (µg/cig)	38.9	4.1	47.0	30.8	21%	29.7	4.0	37.4	21.9	26%
1,3-butadiene (µg/cig)	40.0	4.6	48.9	31.0	22%	30.1	3.3	36.6	23.6	22%
isoprene (µg/cig)	359	38	433	285	21%	272	30	331	212	22%
styrene (µg/cig)	7.1	0.5	8.0	6.2	13%	2.0	0.6	3.2	0.7	63%
toluene (µg/cig)	63.9	5.5	74.8	53.0	17%	39.4	8.5	56.0	22.8	42%
hydrogen cyanide (µg/cig)	122.9	8.6	139.9	106.0	14%	56	4	64	48	14%
nitric oxide (µg/cig)	295	14	323	267	9%	149	9	168	130	12%
nitrogen oxides (µg/cig)	308	16	340	277	10%	-	-	-	-	-
formaldehyde (µg/cig)	20.8	3.7	28.0	13.7	34%	9.6	2.1	13.6	5.6	42%
ammonia (µg/cig)	13.4	0.6	14.6	12.1	9%	-	-	-	-	-
1-aminonaphthalene (ng/cig)	17.6	2.2	21.9	13.2	25%	-	-	-	-	-
2-aminonaphthalene (ng/cig)	11.3	0.8	12.8	9.8	13%	-	-	-	-	-
3-aminobiphenyl (ng/cig)	2.86	0.21	3.28	2.45	14%	-	-	-	-	-
4-aminobiphenyl (ng/cig)	2.17	0.14	2.44	1.91	12%	-	-	-	-	-
benzo[a]pyrene (ng/cig)	6.95	0.33	7.60	6.29	9%	5.19	0.21	5.60	4.78	8%
benz[a]anthracene (ng/cig)	-	-	-	-	-	9.54	0.67	10.87	8.22	14%
catechol (µg/cig)	37.6	3.0	43.4	31.8	15%	-	-	-	-	-
m & p-cresols (µg/cig)	7.8	0.7	9.2	6.4	18%	-	-	-	-	-
o-cresol (µg/cig)	3.20	0.34	3.87	2.53	21%	-	-	-	-	-
hydroquinone (µg/cig)	40.3	2.9	45.9	34.7	14%	-	-	-	-	-
phenol (µg/cig)	10.4	1.6	13.5	7.3	30%	-	-	-	-	-
resorcinol (µg/cig)	0.72	0.20	1.11	0.32	55%	-	-	-	-	-
pyridine (µg/cig)	7.6	0.8	9.1	6.1	20%	-	-	-	-	-
quinoline (µg/cig)	0.30	0.02	0.34	0.25	15%	-	-	-	-	-
NNN (ng/cig)	115.4	14.9	144.7	86.2	25%	87.6	6.8	100.9	74.2	15%
NNK (ng/cig)	91.7	16.6	124.2	59.1	35%	65.6	8.5	82.2	49.0	25%
NAT (ng/cig)	132.4	16.2	164.1	100.6	24%	80.4	5.8	91.9	69.0	14%
NAB (ng/cig)	25.7	6.7	38.9	12.6	51%	9.5	0.8	11.1	7.9	17%
cadmium (ng/cig)	64.4	2.9	70.0	58.8	9%	-	-	-	-	-
lead (ng/cig)	36.7	1.5	39.6	33.7	8%	-	-	-	-	-
mercury (ng/cig)	5.5	0.5	6.5	4.5	19%	-	-	-	-	-
arsenic (ng/cig)	4.7	0.8	6.2	3.1	33%	-	-	-	-	-

[1]Standard error = standard deviation of means. 95% CI = +/- (1.96)(standard error). [2]Smoke constituents without entries were not monitored in all 9 production samples.

These two examples of smoke constituent yields variation support the premise that the predicted yields and prediction intervals are valid options for providing smoke constituent yield information for conventional cigarette brands represented in that study design. The 95% prediction intervals generated from the regression functions provide reasonable expectations of the variation for brands at some average tar, nicotine, or carbon monoxide yield level. As noted before, flue-curing practices are in transition in the U.S. domestic market. This should be reflected in smoke TSNA yield reductions for U.S.-sourced products as these tobaccos are blended into tobacco leaf inventories over

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the next several years.

(4) *Constituents are analyzed by a 'fixed' laboratory.* As there are currently no universally recognized and validated smoke constituent analyses methods, determining smoke constituents yields in a single laboratory or only among laboratories where inter-laboratory-validated methods are used would provide prediction consistency. Benchmarking utility can be severely compromised when constituents are analyzed in different laboratories at different times without method standardization. To illustrate the potential for inconsistencies, Purkis et al (2003) compared ISO-smoke constituent yields for three brands tested by six laboratories. Each laboratory used its own internally validated methods. All laboratories reported the same relative ranking of brands' constituent yields, but there were significant differences among laboratories for particular constituent yields. Ratios of highest to lowest inter-laboratory yields ranged from 1.2 (tar) to 10.0 (quinoline), with an average ratio of 0.8 for all constituents by all laboratories. In contrast, within-laboratory measured constituent yield %CV's were 6% to 9%.

A benchmark approach has the potential to provide reliable predicted smoke constituent yield information, as demonstrated by this study. Differences between predicted and measured yields should be assessed in the context of reasonable analytical variations and short- and medium-term product variations. Benchmarking study design should include a validation process. The split-sample design used in this study was one approach to independently validate the functional relationships. The separate validation brand set was used to assess the relationships through respective prediction errors. Those prediction errors provided guidance on the robustness of the

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benchmark study design. A significant number of validation brands having constituent yields outside the predictive intervals would indicate the model was inappropriate or based on an inadequate representation of market products. By successively adding new brands to the benchmark exploratory and validation brand sets over time, the functional relationship base can be expanded for more accurate prediction of constituent yields. Finally, these data and predictions are limited to machine-smoking only.

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Appendix 1. Results of ISO-method mainstream smoke constituent yields for exploratory brands (E1-E39) and validation brands (V1-V9) [mean ± standard deviation]

Brand Code (1)	Brand / Region (2)	tar (mg/cig)	nicotine (mg/cig)	carbon monoxide (mg/cig)	acetaldehyde (µg/cig)	acetone (µg/cig)	acrolein (µg/cig)	butyraldehyde (µg/cig)	crotonaldehyde (µg/cig)	methyl ethyl ketone (µg/cig)	propionaldehyde (µg/cig)
E1	L & M KS F HP / EU	12.6 ± 0.6	0.81 ± 0.03	11.5 ± 0.5	598 ± 5	330 ± 12	57.6 ± 3.0	40.8 ± 2.1	23.3 ± 0.9	74.5 ± 3.7	59.3 ± 2.8
E2	Merit KS F HP / EU	7.0 ± 0.4	0.54 ± 0.03	8.1 ± 0.5	384 ± 20	224 ± 5	35.8 ± 2.1	25.8 ± 1.5	10.0 ± 1.1	46.1 ± 1.9	36.4 ± 2.7
E3	Marlboro KS F HP (Norway) / EU	13.2 ± 0.7	0.93 ± 0.05	11.3 ± 0.8	540 ± 85	287 ± 34	51.0 ± 7.7	33.9 ± 5.2	19.5 ± 3.2	65.6 ± 8.9	50.2 ± 7.1
E4	Chesterfield INTL KS F HP ULt / EU	3.4 ± 0.2	0.30 ± 0.01	3.4 ± 0.2	148 ± 10	108 ± 5	12.5 ± 0.9	11.4 ± 0.7	NQ ± NQ	17.6 ± 0.9	14.3 ± 1.3
E5	Parliament 100 F SP / CEMA	10.2 ± 0.4	0.77 ± 0.04	10.2 ± 0.5	409 ± 41	201 ± 29	31.4 ± 5.9	20.9 ± 3.0	6.6 ± 1.3	31.8 ± 5.8	33.6 ± 5.0
E6	Philip Morris One KS F HP / EU	1.6 ± 0.2	0.16 ± 0.01	2.0 ± 0.2	76 ± 12	65 ± 7	5.4 ± 1.1	6.2 ± 1.1	NQ ± NQ	8.0 ± 1.5	7.1 ± 0.9
E7	Marlboro Long Size F HP (Argentina) / Latin America	13.9 ± 0.5	1.00 ± 0.04	13.4 ± 0.6	626 ± 36	344 ± 13	61.9 ± 3.6	40.3 ± 1.8	24.9 ± 1.6	76.4 ± 4.7	59.5 ± 1.9
E8	Parliament KS F HP Lt (Japan) / US Export	7.0 ± 0.4	0.57 ± 0.03	7.5 ± 0.3	218 ± 41	117 ± 24	14.8 ± 2.7	11.0 ± 1.8	NQ ± NQ	16.6 ± 3.7	15.8 ± 3.3
E9	L & M KS F HP Lt / EU	8.4 ± 0.4	0.58 ± 0.03	8.4 ± 0.3	397 ± 21	220 ± 8	35.6 ± 1.9	26.0 ± 1.8	10.9 ± 0.9	45.1 ± 1.9	36.1 ± 1.9
E10	Marlboro Long Size F HP (Venezuela) / Latin America	13.1 ± 0.8	0.91 ± 0.05	11.1 ± 0.7	504 ± 68	276 ± 33	45.7 ± 6.0	32.2 ± 3.8	17.8 ± 3.5	59.3 ± 7.6	48.2 ± 6.5
E11	Marlboro KS F HP (Taiwan) / US Export	11.6 ± 0.9	0.93 ± 0.04	9.6 ± 0.6	384 ± 46	203 ± 22	32.1 ± 3.8	21.9 ± 2.8	8.0 ± 1.4	37.2 ± 5.0	33.3 ± 3.3
E12	F6 KS F HP Lt / EU	8.4 ± 0.4	0.71 ± 0.04	8.6 ± 0.4	363 ± 53	209 ± 20	33.0 ± 5.3	25.3 ± 2.9	10.1 ± 1.6	46.2 ± 4.7	34.1 ± 3.5
E13	Virginia Slims 100 F HP Men 1mg (Japan) / US Export	0.9 ± 0.1	0.10 ± 0.01	1.1 ± 0.1	32 ± 12	46 ± 6	NQ ± NQ	NQ ± NQ	BDL ± BDL	NQ ± NQ	NQ ± NQ
E14	Marlboro KS F HP Lt (Germany/Great Britain) / EU	5.9 ± 0.3	0.53 ± 0.03	6.4 ± 0.2	323 ± 43	182 ± 13	30.1 ± 4.2	21.4 ± 2.6	7.0 ± 1.1	36.3 ± 3.6	30.7 ± 3.5
E15	Virginia Slims 100 F HP ULt Men (Japan) / US Export	2.7 ± 0.2	0.23 ± 0.02	3.1 ± 0.3	114 ± 25	96 ± 17	8.7 ± 2.1	8.8 ± 1.8	NQ ± NQ	13.3 ± 3.0	11.0 ± 2.0
E16	Parliament 100 F SP Lt / US	11.6 ± 0.6	0.95 ± 0.05	11.4 ± 0.6	481 ± 29	239 ± 10	38.6 ± 2.8	26.1 ± 1.8	8.8 ± 0.9	44.0 ± 2.6	41.0 ± 3.4
E17	Marlboro KS F SP / US	14.2 ± 0.5	1.02 ± 0.04	12.9 ± 0.6	601 ± 43	318 ± 12	55.4 ± 5.8	39.7 ± 3.6	20.1 ± 2.4	71.7 ± 6.3	55.7 ± 4.6
E18	Marlboro 100 F HP / EU	12.6 ± 0.5	0.93 ± 0.04	11.6 ± 0.6	554 ± 33	291 ± 18	51.3 ± 3.4	35.8 ± 2.6	17.4 ± 1.4	67.3 ± 5.1	51.5 ± 3.0
E19	Marlboro 100 F HP Lt (Germany) / EU	6.9 ± 0.2	0.63 ± 0.02	7.1 ± 0.4	311 ± 39	178 ± 14	27.5 ± 4.7	19.5 ± 2.3	6.0 ± 1.1	34.4 ± 3.5	28.6 ± 3.4
E20	SG Ventil Regular F SP / EU	11.1 ± 0.5	0.67 ± 0.03	9.1 ± 0.4	488 ± 45	267 ± 22	44.3 ± 4.7	33.7 ± 2.3	20.5 ± 1.8	61.8 ± 4.6	47.0 ± 4.5
E21	Muratti KS F HP ULt 1mg / CEMA	1.0 ± 0.2	0.11 ± 0.01	1.3 ± 0.1	57 ± 11	59 ± 9	3.6 ± 0.7	5.4 ± 0.8	NQ ± NQ	6.6 ± 0.6	5.7 ± 0.6
E22	Diana KS F SP Specially Mild / EU	9.7 ± 0.3	0.74 ± 0.03	8.8 ± 0.3	390 ± 63	223 ± 26	39.1 ± 8.1	27.7 ± 4.5	13.9 ± 2.4	48.7 ± 7.2	39.2 ± 5.6
E23	Muratti Ambassador KS F HP / EU	8.4 ± 0.4	0.65 ± 0.05	7.5 ± 0.4	288 ± 43	146 ± 22	19.7 ± 3.7	15.4 ± 1.9	4.9 ± 0.9	24.7 ± 4.0	23.6 ± 3.4
E24	Merit KS F SP ULt / US	4.9 ± 0.2	0.46 ± 0.03	5.9 ± 0.3	254 ± 50	165 ± 28	20.4 ± 4.7	19.5 ± 3.9	5.8 ± 1.7	31.1 ± 6.1	25.0 ± 4.6
E25	Petra Regular F HP / CEMA	13.3 ± 0.6	0.85 ± 0.03	11.2 ± 0.4	515 ± 71	287 ± 34	43.8 ± 6.1	37.6 ± 4.3	20.7 ± 3.5	69.7 ± 9.0	49.2 ± 6.4
E26	Marlboro KS F HP ULt Men / US	5.9 ± 0.5	0.49 ± 0.04	6.9 ± 0.4	277 ± 48	170 ± 25	25.7 ± 4.0	20.5 ± 3.6	6.7 ± 1.6	33.0 ± 5.4	26.9 ± 3.5
E27	Diana KS F HP ULt / EU	3.0 ± 0.2	0.29 ± 0.02	3.3 ± 0.2	146 ± 16	103 ± 12	13.0 ± 2.0	10.9 ± 1.2	NQ ± NQ	16.8 ± 2.0	14.6 ± 1.8
E28	Marlboro KS F HP (Malaysia) / Asia Pacific	14.4 ± 0.5	1.03 ± 0.04	11.9 ± 0.7	604 ± 28	316 ± 19	58.7 ± 3.5	43.8 ± 3.5	23.3 ± 2.1	69.2 ± 5.1	60.4 ± 3.5
E29	Marlboro KS F HP 25's (Australia) / US Export	13.1 ± 0.6	0.98 ± 0.05	12.3 ± 0.9	517 ± 45	291 ± 29	47.4 ± 3.6	36.2 ± 4.5	17.6 ± 2.7	62.6 ± 6.9	49.7 ± 3.6
E30	Marlboro KS F HP (Japan) / Japan	12.1 ± 0.5	1.04 ± 0.05	11.2 ± 0.6	481 ± 31	257 ± 14	36.6 ± 2.8	23.9 ± 2.2	9.2 ± 1.1	46.2 ± 3.9	39.5 ± 2.6
E31	Longbeach One KS F HP / Australia	1.2 ± 0.1	0.15 ± 0.02	1.6 ± 0.1	113 ± 19	96 ± 7	8.7 ± 1.5	8.2 ± 1.0	NQ ± NQ	15.0 ± 2.4	11.1 ± 1.7
E32	Chesterfield Originals KS F HP Lt / EU	8.0 ± 0.5	0.59 ± 0.02	8.3 ± 0.4	432 ± 42	243 ± 19	41.3 ± 3.1	27.0 ± 2.5	12.4 ± 1.1	51.7 ± 5.1	40.4 ± 3.0
E33	Philip Morris 100 F HP Super Lt / EU	3.3 ± 0.3	0.33 ± 0.02	3.5 ± 0.2	161 ± 11	115 ± 10	13.0 ± 1.0	12.2 ± 0.7	NQ ± NQ	19.4 ± 2.2	14.9 ± 1.2
E34	Chesterfield Originals KS F HP / EU	11.9 ± 0.5	0.80 ± 0.04	11.7 ± 0.7	586 ± 36	319 ± 19	57.0 ± 3.7	36.8 ± 2.6	22.6 ± 2.3	74.7 ± 5.9	53.5 ± 4.2
E35	Marlboro KS F HP Medium / EU	9.6 ± 0.4	0.72 ± 0.03	10.0 ± 0.7	458 ± 36	262 ± 15	41.2 ± 2.6	29.2 ± 1.4	13.5 ± 0.9	57.9 ± 3.5	42.9 ± 3.8
E36	Virginia Slims 100 F HP ULt Men / US	5.1 ± 0.3	0.45 ± 0.02	4.9 ± 0.3	207 ± 34	139 ± 17	20.5 ± 3.7	14.4 ± 1.8	4.6 ± 1.0	24.6 ± 3.9	20.0 ± 2.4
E37	Marlboro KS F HP ULt / EU	3.0 ± 0.2	0.29 ± 0.01	3.5 ± 0.1	150 ± 5	105 ± 7	11.8 ± 1.0	10.4 ± 0.7	NQ ± NQ	16.5 ± 0.9	14.0 ± 1.1
E38	L & M KS F HP (Malaysia) / Asia Pacific	13.5 ± 0.4	1.01 ± 0.03	10.4 ± 0.3	591 ± 53	292 ± 15	57.2 ± 6.3	39.3 ± 3.5	21.8 ± 2.4	64.3 ± 4.6	54.6 ± 4.7
E39	Marlboro KS F HP Lt (Japan) / Japan	5.9 ± 0.3	0.44 ± 0.02	6.8 ± 0.4	227 ± 22	126 ± 13	16.7 ± 2.2	11.0 ± 1.0	NQ ± NQ	17.8 ± 2.3	18.2 ± 2.5
V1	Marlboro KS F HP Lt (Norway) / EU	8.3 ± 0.4	0.69 ± 0.04	8.5 ± 0.4	363 ± 41	201 ± 17	30.8 ± 4.6	24.7 ± 3.7	10.9 ± 1.7	41.8 ± 4.2	32.8 ± 3.9
V2	Raffles 100 F HP / EU	12.3 ± 0.5	1.19 ± 0.10	12.8 ± 0.7	643 ± 40	335 ± 18	60.3 ± 4.5	47.5 ± 3.3	28.3 ± 2.9	78.0 ± 6.1	56.4 ± 3.3
V3	Chesterfield KS F HP Lt / EU	6.3 ± 0.2	0.54 ± 0.04	7.3 ± 0.3	319 ± 17	176 ± 10	27.6 ± 1.5	20.9 ± 1.5	8.9 ± 1.1	34.5 ± 2.8	28.1 ± 1.7
V4	Philip Morris KS F HP Super Lt / EU	4.1 ± 0.4	0.40 ± 0.03	4.0 ± 0.3	147 ± 16	97 ± 9	12.1 ± 1.6	11.4 ± 1.2	NQ ± NQ	15.9 ± 1.7	13.8 ± 1.6
V5	Merit KS F SP Ultima / US	1.3 ± 0.2	0.13 ± 0.01	2.4 ± 0.1	129 ± 13	87 ± 5	9.7 ± 0.8	10.2 ± 1.6	NQ ± NQ	13.4 ± 1.1	11.8 ± 1.1
V6	Marlboro 100 F HP Lt / US	9.6 ± 0.4	0.80 ± 0.05	10.7 ± 0.3	461 ± 61	262 ± 30	42.6 ± 6.4	33.1 ± 4.2	15.8 ± 2.6	53.9 ± 6.1	42.6 ± 4.5
V7	Peter Jackson KS F HP Men / Australia	7.4 ± 0.4	0.72 ± 0.06	8.3 ± 0.4	396 ± 31	224 ± 15	39.9 ± 3.2	27.0 ± 1.6	16.5 ± 1.9	48.4 ± 3.5	35.4 ± 2.6
V8	Marlboro KS F HP (Mexico) / Latin America	13.2 ± 0.5	1.13 ± 0.06	12.1 ± 0.5	520 ± 49	298 ± 26	50.7 ± 5.3	35.7 ± 3.2	22.8 ± 2.8	62.8 ± 6.4	47.8 ± 4.3
V9	Marlboro KS F HP (Brazil) / Latin America	12.1 ± 0.7	0.97 ± 0.09	11.4 ± 0.5	527 ± 64	288 ± 25	47.7 ± 6.4	36.9 ± 4.7	22.8 ± 3.0	64.2 ± 5.4	48.0 ± 5.4
R1	1R4F Kentucky Reference	9.1 ± 0.4	0.73 ± 0.04	11.6 ± 0.6	574 ± 57	312 ± 22	46.3 ± 4.8	38.8 ± 3.6	14.9 ± 1.5	75.0 ± 6.4	55.9 ± 5.6
R2	1R4F Kentucky Reference	8.9 ± 0.4	0.77 ± 0.07	12.2 ± 0.5	518 ± 43	282 ± 21	38.5 ± 3.4	36.1 ± 5.5	15.4 ± 1.5	63.8 ± 5.4	48.1 ± 3.8

(1) E = exploratory brands, V = validation brands, R = reference cigarettes. (2) Brand names are trademarks of Philip Morris USA Inc., Philip Morris Products S.A., Philip Morris Limited (Australia), Philip Morris CR, A.S., Tabaqueria, S.A., or F6 Cigarettenfabrik Dresden GmbH, De. (3) N-nitrosonornicotine (NNN), 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanatabine (NAT), N-nitrosoanabasine (NAB). (4) BDL = below the detection limit, NQ = below the limit for quantitation. (5) HP = hard pack, SP = soft pack, F = filter, Lt = lights, ULt = ultra lights, KS = king size, Men = menthol.

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Appendix 1. Results of ISO-method mainstream smoke constituent yields for exploratory brands (E1-E39) and validation brands (V1-V9) [mean ± standard deviation]

Brand Code (1)	formaldehyde (µg/cig)	acrylonitrile (µg/cig)	benzene (µg/cig)	1,3-butadiene (µg/cig)	isoprene (µg/cig)	styrene (µg/cig)	toluene (µg/cig)	ammonia (µg/cig)	hydrogen cyanide (µg/cig)	nitric oxide (µg/cig)	nitrogen oxides (µg/cig)	1-aminonaphthalene (ng/cig)	2-aminonaphthalene (ng/cig)
E1	42.8 ± 2.4	10.1 ± 0.7	44.6 ± 2.6	45.5 ± 3.4	356 ± 18	10.5 ± 0.7	69.9 ± 5.3	17.5 ± 1.3	116.6 ± 7.1	153 ± 11	155 ± 10	17.5 ± 3.1	10.7 ± 1.6
E2	20.9 ± 3.4	6.9 ± 0.5	32.8 ± 1.4	35.4 ± 1.7	295 ± 13	5.2 ± 0.3	48.7 ± 2.7	11.2 ± 1.0	61.6 ± 4.5	141 ± 14	145 ± 17	11.6 ± 1.0	7.6 ± 0.7
E3	38.2 ± 7.6	10.7 ± 0.4	43.6 ± 1.5	45.7 ± 2.9	385 ± 21	9.3 ± 0.6	67.6 ± 2.9	17.8 ± 1.5	114.4 ± 8.0	156 ± 16	158 ± 16	18.2 ± 2.1	11.1 ± 1.2
E4	6.7 ± 2.1	2.8 ± 0.3	17.5 ± 0.7	17.9 ± 1.4	150 ± 11	2.5 ± 0.3	24.2 ± 1.8	5.6 ± 0.5	13.4 ± 2.0	59 ± 5	61 ± 5	7.8 ± 1.1	4.7 ± 0.7
E5	23.3 ± 2.9	5.8 ± 0.4	23.2 ± 1.9	39.0 ± 1.9	286 ± 23	2.7 ± 0.2	28.7 ± 2.6	17.8 ± 1.5	58.5 ± 6.8	184 ± 18	186 ± 18	19.8 ± 2.8	11.9 ± 1.7
E6	3.4 ± 0.7	1.8 ± 0.2	11.0 ± 0.9	12.8 ± 1.4	130 ± 12	1.4 ± 0.1	13.9 ± 1.6	4.4 ± 0.5	6.8 ± 0.8	67 ± 8	69 ± 8	5.9 ± 0.7	3.7 ± 0.4
E7	52.1 ± 5.2	11.3 ± 0.7	44.1 ± 2.1	48.5 ± 2.8	475 ± 34	10.2 ± 0.7	66.0 ± 2.6	16.2 ± 1.8	132.5 ± 4.5	177 ± 11	182 ± 11	15.7 ± 2.6	9.9 ± 1.6
E8	10.8 ± 1.2	3.6 ± 0.4	15.1 ± 1.3	23.9 ± 0.8	195 ± 10	1.9 ± 0.3	20.5 ± 1.4	12.7 ± 1.1	28.7 ± 2.9	161 ± 14	162 ± 14	14.8 ± 1.2	9.4 ± 0.5
E9	24.8 ± 4.8	7.0 ± 0.3	34.7 ± 1.3	34.6 ± 1.4	271 ± 11	5.9 ± 0.6	52.3 ± 2.4	11.5 ± 1.7	58.3 ± 4.5	115 ± 15	117 ± 16	13.8 ± 2.1	8.6 ± 1.2
E10	35.2 ± 4.5	9.8 ± 0.3	37.7 ± 1.2	43.8 ± 2.1	414 ± 20	7.7 ± 0.4	58.9 ± 4.1	19.7 ± 1.9	112.8 ± 5.8	148 ± 11	151 ± 12	20.4 ± 2.6	12.1 ± 1.2
E11	24.1 ± 5.9	5.9 ± 0.4	26.6 ± 1.8	36.4 ± 0.7	313 ± 17	3.4 ± 0.4	37.2 ± 3.2	22.2 ± 0.9	99.5 ± 7.1	231 ± 26	239 ± 26	21.4 ± 2.3	13.4 ± 1.7
E12	31.2 ± 6.3	4.9 ± 0.3	35.0 ± 2.8	35.4 ± 3.0	276 ± 18	5.0 ± 0.3	49.5 ± 6.1	10.0 ± 0.7	73.2 ± 5.3	58 ± 10	60 ± 10	10.7 ± 2.2	6.5 ± 1.0
E13	1.6 ± 0.6	NQ ± NQ	6.3 ± 0.5	6.4 ± 0.2	74 ± 3	NQ ± NQ	NQ ± NQ	3.2 ± 0.3	3.4 ± 0.5	31 ± 3	32 ± 3	3.2 ± 0.5	2.2 ± 0.3
E14	22.1 ± 6.7	3.7 ± 0.3	25.9 ± 1.1	30.8 ± 1.6	270 ± 16	3.4 ± 0.3	35.6 ± 3.0	9.3 ± 0.6	45.6 ± 4.4	78 ± 16	81 ± 15	10.7 ± 0.8	6.9 ± 0.7
E15	3.5 ± 1.0	1.7 ± 0.1	16.0 ± 1.5	16.1 ± 1.6	164 ± 8	1.3 ± 0.2	21.5 ± 3.2	6.3 ± 0.5	15.4 ± 1.7	81 ± 13	83 ± 14	8.9 ± 1.7	5.6 ± 0.8
E16	29.9 ± 6.7	5.3 ± 0.3	26.2 ± 1.9	37.7 ± 1.4	330 ± 15	2.7 ± 0.4	35.0 ± 4.2	22.2 ± 1.3	106.5 ± 8.0	223 ± 16	231 ± 15	21.5 ± 2.2	13.5 ± 1.6
E17	33.0 ± 8.5	10.0 ± 0.8	45.2 ± 3.1	50.8 ± 3.1	484 ± 31	8.8 ± 0.7	68.8 ± 5.5	25.9 ± 0.6	194.4 ± 12.7	242 ± 14	254 ± 15	22.5 ± 4.1	13.8 ± 2.1
E18	36.6 ± 8.8	8.7 ± 0.7	43.8 ± 3.4	45.9 ± 1.2	411 ± 17	7.3 ± 0.5	66.0 ± 5.6	21.7 ± 0.7	120.2 ± 12.9	153 ± 14	159 ± 14	22.4 ± 3.8	13.3 ± 1.0
E19	13.5 ± 3.0	4.8 ± 0.6	30.2 ± 2.5	31.9 ± 1.8	299 ± 17	3.7 ± 0.4	41.2 ± 4.9	10.4 ± 0.2	51.0 ± 2.9	87 ± 9	90 ± 10	14.9 ± 2.2	8.9 ± 1.6
E20	41.7 ± 5.3	8.2 ± 0.6	31.8 ± 2.2	35.2 ± 2.9	281 ± 15	9.4 ± 0.8	47.0 ± 3.6	12.7 ± 1.2	107.1 ± 6.7	81 ± 11	85 ± 11	13.7 ± 2.4	8.5 ± 0.8
E21	2.2 ± 0.3	NQ ± NQ	6.1 ± 0.5	6.6 ± 0.4	70 ± 3	0.9 ± 0.4	NQ ± NQ	3.1 ± 0.3	4.3 ± 1.0	28 ± 5	29 ± 5	5.4 ± 0.8	3.4 ± 0.5
E22	24.3 ± 4.8	8.3 ± 0.5	37.6 ± 2.2	36.8 ± 2.4	313 ± 21	8.7 ± 0.5	55.2 ± 3.3	12.9 ± 1.3	99.5 ± 7.1	101 ± 9	104 ± 10	15.2 ± 2.9	10.2 ± 1.7
E23	18.9 ± 2.0	3.6 ± 0.2	17.6 ± 0.6	25.0 ± 0.9	182 ± 8	2.7 ± 1.1	24.2 ± 1.6	11.7 ± 1.1	42.7 ± 3.9	55 ± 3	57 ± 3	16.6 ± 3.6	10.0 ± 1.5
E24	8.5 ± 1.3	4.4 ± 0.3	23.0 ± 1.2	23.0 ± 1.4	233 ± 16	4.0 ± 0.5	30.7 ± 3.3	8.8 ± 0.9	51.4 ± 5.8	115 ± 17	119 ± 19	14.4 ± 2.5	9.3 ± 1.0
E25	41.8 ± 7.9	9.5 ± 0.5	40.0 ± 2.6	38.5 ± 1.5	307 ± 10	11.6 ± 0.5	62.8 ± 5.3	17.2 ± 1.0	126.0 ± 9.7	86 ± 7	89 ± 7	16.8 ± 2.0	10.7 ± 1.4
E26	9.7 ± 1.6	5.4 ± 0.2	28.2 ± 1.2	28.2 ± 1.6	270 ± 13	3.7 ± 0.7	37.5 ± 2.0	10.9 ± 0.6	64.2 ± 3.2	137 ± 8	142 ± 8	16.0 ± 3.3	10.5 ± 1.4
E27	6.0 ± 0.9	2.3 ± 0.3	15.4 ± 1.3	14.9 ± 0.9	136 ± 8	2.1 ± 0.3	19.1 ± 2.2	5.3 ± 0.6	15.2 ± 1.8	38 ± 5	39 ± 5	8.9 ± 1.2	5.8 ± 0.9
E28	28.1 ± 2.4	11.7 ± 1.2	44.1 ± 4.5	43.9 ± 2.2	403 ± 30	11.6 ± 1.2	66.8 ± 7.9	29.0 ± 1.1	185.5 ± 9.1	216 ± 23	226 ± 24	27.0 ± 3.2	17.2 ± 0.9
E29	26.2 ± 0.8	10.5 ± 0.7	42.3 ± 2.4	43.3 ± 2.8	439 ± 20	9.4 ± 0.8	63.1 ± 4.3	23.3 ± 0.6	166.7 ± 11.2	191 ± 26	201 ± 27	23.4 ± 3.4	15.2 ± 2.2
E30	29.4 ± 2.0	6.1 ± 0.4	24.5 ± 1.4	36.1 ± 1.3	278 ± 13	4.3 ± 0.6	34.2 ± 2.8	16.8 ± 0.7	77.5 ± 8.6	170 ± 16	179 ± 20	23.8 ± 3.0	15.3 ± 1.4
E31	3.5 ± 0.6	1.3 ± 0.1	11.2 ± 0.6	11.3 ± 0.7	94 ± 7	1.7 ± 0.5	14.5 ± 1.6	NQ ± NQ	5.8 ± 0.7	13 ± 2	13 ± 3	4.4 ± 0.7	2.9 ± 0.4
E32	21.2 ± 2.5	6.5 ± 0.3	29.7 ± 1.3	33.2 ± 0.5	272 ± 8	4.6 ± 0.7	44.7 ± 2.3	12.0 ± 0.4	62.1 ± 5.0	91 ± 11	96 ± 12	14.8 ± 1.1	10.1 ± 0.4
E33	6.2 ± 1.1	2.6 ± 0.2	16.7 ± 0.9	17.2 ± 0.5	156 ± 5	2.5 ± 0.4	22.7 ± 2.9	6.3 ± 0.2	16.2 ± 1.6	60 ± 11	62 ± 12	11.2 ± 0.7	7.8 ± 0.4
E34	33.2 ± 2.5	9.9 ± 0.5	37.6 ± 2.1	42.9 ± 2.9	357 ± 10	9.6 ± 0.8	58.0 ± 4.0	16.8 ± 0.9	130.0 ± 10.5	118 ± 9	123 ± 10	16.9 ± 1.4	10.8 ± 1.0
E35	26.7 ± 1.1	6.9 ± 0.4	33.0 ± 1.6	34.4 ± 1.0	284 ± 6	6.2 ± 0.6	50.5 ± 2.8	13.9 ± 0.9	90.4 ± 8.2	123 ± 12	130 ± 13	16.7 ± 1.4	11.8 ± 1.0
E36	9.1 ± 1.4	3.7 ± 0.4	19.7 ± 1.0	21.2 ± 1.2	199 ± 12	2.9 ± 0.4	28.5 ± 2.0	10.2 ± 0.9	35.3 ± 5.8	111 ± 15	114 ± 15	14.0 ± 1.7	9.6 ± 1.2
E37	5.5 ± 0.6	2.2 ±											

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		0.1	14.7 ± 0.6	16.1 ± 0.9	150 ± 6	2.1 ± 0.5	19.4 ± 0.7	5.3 ± 0.5	13.6 ± 1.1	42 ± 3	44 ± 3	9.1 ± 0.5	6.3 ± 0.3
E38	35.5 ± 4.6	10.5 ± 0.4	38.5 ± 1.5	45.2 ± 1.9	412 ± 15	9.9 ± 0.9	61.8 ± 2.4	20.4 ± 0.9	151.1 ± 11.5	179 ± 16	188 ± 18	25.8 ± 3.9	16.7 ± 1.5
E39	14.1 ± 2.1	2.4 ± 0.2	12.8 ± 0.9	20.7 ± 1.0	132 ± 7	1.9 ± 0.5	18.1 ± 1.3	8.9 ± 0.4	23.7 ± 3.1	87 ± 16	90 ± 17	11.7 ± 1.2	7.5 ± 1.1
V1	19.0 ± 3.5	7.4 ± 0.6	30.7 ± 1.9	35.0 ± 2.1	291 ± 19	5.9 ± 0.6	47.8 ± 3.6	14.0 ± 1.0	68.3 ± 3.7	106 ± 10	113 ± 10	15.6 ± 1.3	9.8 ± 1.1
V2	40.6 ± 6.7	11.1 ± 0.8	44.4 ± 2.8	54.1 ± 5.6	466 ± 43	10.4 ± 1.4	67.5 ± 3.3	12.4 ± 1.2	134.8 ± 11.7	118 ± 14	126 ± 13	18.1 ± 3.2	9.8 ± 1.3
V3	17.3 ± 1.9	5.5 ± 0.2	25.4 ± 1.5	29.3 ± 2.6	244 ± 21	4.6 ± 0.7	38.2 ± 2.5	9.7 ± 1.4	52.8 ± 5.5	62 ± 7	67 ± 7	12.6 ± 2.0	7.5 ± 1.0
V4	8.0 ± 2.0	3.2 ± 0.3	17.0 ± 1.1	19.4 ± 0.9	179 ± 11	2.9 ± 0.6	25.0 ± 2.0	7.3 ± 0.7	23.3 ± 2.8	53 ± 6	56 ± 6	11.0 ± 0.6	6.9 ± 0.4
V5	4.0 ± 0.5	2.8 ± 0.1	11.9 ± 0.6	13.5 ± 0.5	134 ± 5	1.9 ± 0.4	17.7 ± 1.1	3.1 ± 0.5	19.4 ± 1.9	45 ± 8	48 ± 8	4.3 ± 0.7	2.7 ± 0.4
V6	18.2 ± 1.5	9.7 ± 0.5	39.7 ± 2.0	42.3 ± 2.6	383 ± 22	6.5 ± 0.9	60.0 ± 2.6	16.9 ± 1.3	112.8 ± 7.1	190 ± 14	202 ± 16	21.5 ± 4.3	13.6 ± 2.0
V7	41.2 ± 5.4	6.3 ± 0.5	30.8 ± 2.2	38.7 ± 2.3	297 ± 17	7.3 ± 0.7	43.8 ± 3.4	7.5 ± 0.4	65.4 ± 7.4	47 ± 5	51 ± 5	10.6 ± 1.5	5.6 ± 0.6
V8	34.8 ± 5.9	11.3 ± 0.6	43.1 ± 0.7	51.6 ± 2.4	448 ± 26	10.6 ± 0.8	64.4 ± 2.3	18.9 ± 0.9	137.1 ± 12.9	149 ± 13	160 ± 16	20.7 ± 2.0	11.8 ± 1.4
V9	32.4 ± 4.6	10.5 ± 0.7	39.6 ± 1.7	47.4 ± 1.9	364 ± 17	11.1 ± 0.5	63.6 ± 3.6	15.6 ± 0.6	127.8 ± 10.7	119 ± 10	125 ± 12	18.2 ± 2.5	10.4 ± 1.4
R1	26.4 ± 7.3	8.3 ± 0.8	40.5 ± 2.6	42.8 ± 3.3	397 ± 19	7.1 ± 0.2	65.2 ± 5.0	13.4 ± 0.5	130.2 ± 10.5	317 ± 21	331 ± 22	20.0 ± 4.5	11.9 ± 2.3
R2	19.3 ± 1.8	9.2 ± 0.5	37.3 ± 3.1	39.0 ± 2.3	342 ± 27	7.7 ± 0.3	61.2 ± 5.4	14.1 ± 1.0	121.3 ± 10.8	283 ± 25	296 ± 25	18.4 ± 1.4	11.7 ± 0.5

(1) E = exploratory brands, V = validation brands, R = reference cigarettes. (2) Brand names are trademarks of Philip Morris USA Inc., Philip Morris Products S.A., Philip Morris Limited (Australia), Philip Morris CR, A.S., Tabaquera, S.A., or F6 Cigarettenfabrik Dresden GmbH, De. (3) N-nitrosonornicotine (NNN), 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanatabine (NAT), N-nitrosoanabasine (NAB). (4) BDL = below the detection limit, NQ = below the limit for quantitation. (5) HP = hard pack, SP = soft pack, F = filter, Lt = lights, ULt = ultra lights, KS = king size, Men = menthol.

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